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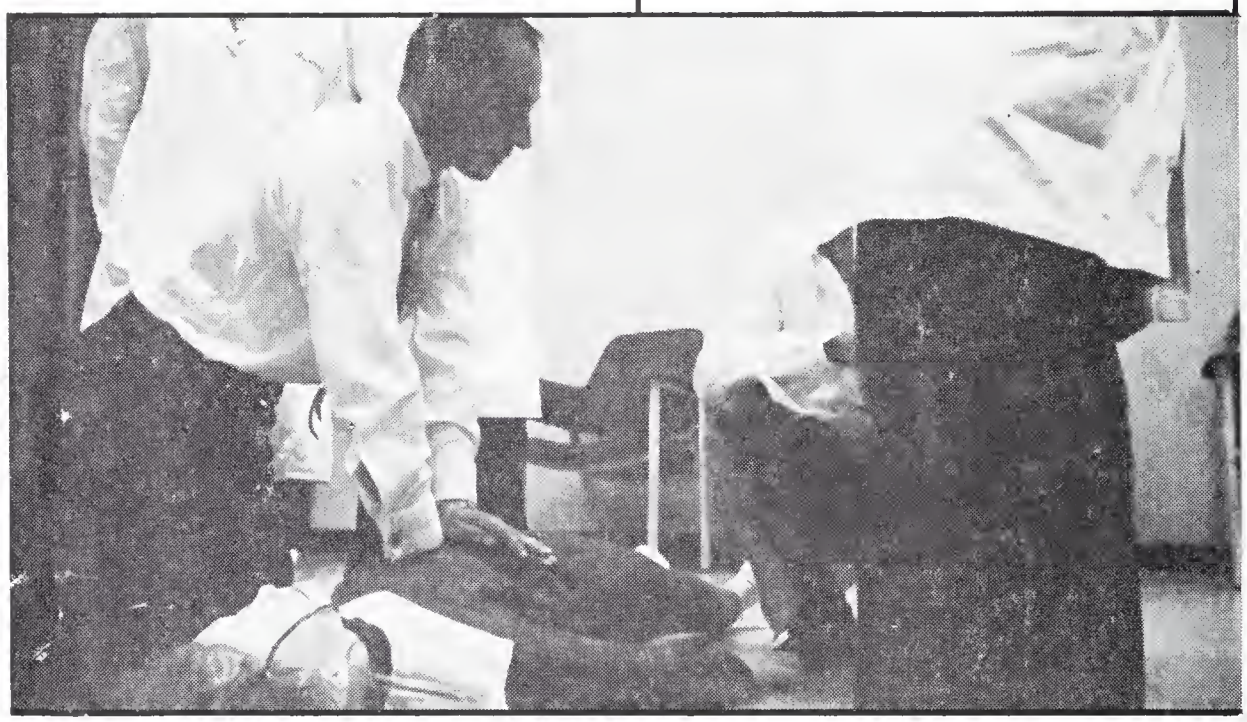

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Editorials

For the Greeks and Romans, the breath and the soul were synonymous. The apprehension of an acutely dyspneic patient is unforgettable. When faced with an unconscious patient, the modern physician's first concern is to maintain an adequate airway. Thus, the primary importance of respiration has always been recognized.

The structure of the lungs is deceptively simple. Nevertheless, understanding of pulmonary function remains far from complete. The physics of gas exchange, the mechanics of breathing and the controlling factors involved in respiration are exceedingly complex. The problem posed by lungs which no longer adequately perform their functions is similarly a complex one. Nevertheless, it is only through an understanding of the physiology of the normal and pathological lung that the physician can rationally approach the problem of pulmonary insufficiency or dyspnea. Accordingly, the article which opens this issue can be extremely valuable to those who must manage the problems of pulmonary disease.

Pulmonary function tests are providing increasing understanding of the disruptions of physiology in the "failing lung." At present, they are still crude tests capable of detecting only gross defects. Moreover, they tell only how the functions of the lungs are impaired. They give little indication of why such impairment exists. Nevertheless, they remain most useful in the management of such problems; for example, bronchodilators may be expected to be useful in obstructive defects and to be of little aid in restrictive or diffusion defects. Moreover, the tests provide objective means of measurement of the improvement seen with various types of therapy. One may expect these tests to assume increasing importance in the assessment and management of disorders of respiration.

Tuberculosis and bronchogenic carcinoma remain two major diseases of the chest. The former is now treated with considerable success. Mr. Gibbs' article provides a clear concise summary of the current management of this problem. However, bronchogenic carcinoma remains a fatal disease. While the ultimate conquest of this condition will depend on its prevention, current cure demands early recognition and surgical excision. Accordingly, constant alertness for this condition and adequate understanding of its investigation are most important.

In a previous issue of this Journal, Mr. D. J. Shepley has suggested how computers may revolutionize modern medicine.[1] The savings in time, errors and money which they provide are making them most attractive in hospital administration. As more and more hospitals use them in administration, a fund of clinical information surpassing that of the most senior clinician will rapidly accumulate. The use of this information in the improvement of diagnoses and choices of investigations and treatments is becoming a major challenge to medicine.

Mr. Nussbaum's paper describes an exercise attempting diagnosis by computer. Such an exercise demanded a careful analysis of the process of medical diagnosis so that the computer could be told exactly what to do. The method of diagnosis chosen depended largely on the form in which the information was available and apparently resembled that used by many senior clinicians. In selecting a diagnosis, the computer first considered the relative incidence of all diseases which could possibly account for the symptoms presented. Then, it considered each aspect of the history individually. If an aspect was relatively common in a given disease, the computer recorded the disease as being a more likely cause of the syndrome. Thus, the diagnosis depended on a comparison of the clinical features of each individual case with a "mental picture" of each disease entity which could possibly give such a presentation. The process of diagnosis involved a consideration of both the epidemiology and the phenomenology of every possible disease.

Mr. Nussbaum's exposition of the problems involved in such an approach provides a better understanding of the problems involved in all medical diagnoses as well as providing a further introduction into an important field of investigation.

The contributors to this issue have provided several fine articles on how diseases may affect the lung's functions. They have shown how two such diseases may be investigated and managed. Finally, there has been a consideration of a revolutionary technique, the use of computers, in the investigation of chest pain. It is hoped that the authors' efforts will prove useful to the reader in understanding and approaching diseases of the lung.

J.E.S

REFERENCE

1. D. J. Shepley, A survey of computers in medicine, University of Toronto Medical Journal, 42, 117-120, 1965.

A student medical journal can aim to achieve different objectives. It can be directed solely to the medical student of that particular institution, with articles gleaned from the standard medical tacts, and quaint homilies on local personages; conversely, the journal can appeal to graduate physicians, as well as to the medical undergraduate, with articles based on comprehensive reviews of the literature and personal research. The experience to the student writer for this latter type of publication is invaluable, not only for the knowledge derived from his extensive reading, but also for the early opportunity of learning to write a scientific paper. To the undergraduate reader this form of journal generally offers the first exposure to the scientific literature (apart from textbooks), and both he and the graduate reader are able to learn of the newer aspects of medicine. The reader may criticise particular articles for lack of direct clinical application, but it is in the realms of etiology and pathophysiology that exciting new advances are being made.

It has been the objective of Volume XLII of the University of Toronto Medical Journal to fulfill these aims. This would have been impossible without the aid of a competent and responsible staff of Associate and Assistant Editors who have earned our grateful thanks.

No journal can exist without its business staff, and to those of our staff who spent many frustrating hours, dealing with the general financial, advertising, and circulation aspects of this Journal, we are indebted. It is to their credit that they persisted in their work, accomplishing during the academic year what, in actual fact, is a twelve month task. Indeed, to achieve an adequate advertising content, it has become evident that the work of the advertising staff, in particular, must be on a year-round basis.

To the editors of next year's Journal, Messrs. S. K. Bernstein and A. G. Logan, we extend our best wishes and are confident that they will achieve the same enjoyment and sense of accomplishment as have the editors of Volume XLII.

J.S.B.
B.E.K.

The Demand and Effort Concept of Dyspnea

E. M. Sellers 6T5
Sirje Sellers 6T5

A. THE REGULATION OF RESPIRATION
B. THE AETIOLOGY OF DYSPNEA

A. The Regulation of Respiration

In recent years, many researchers have been stimulated to investigate the regulation of breathing. As a result, older concepts have been challenged and new theories advanced, but as yet no comprehensive picture of the control of respiration can be presented as proven fact.

Basically, respiration is controlled by rhythmic impulses arising in respiratory centres in the brain stem and descending in alpha motor neurons to activate respiratory muscles. Factors which may alter the impulses which reach the respiratory muscles are central, reflex and chemical.

1. *CENTRAL CONTROL*

The central mechanisms governing respiration have been investigated principally by three methods: experimental surgery, stimulation of small areas of the brain and microelectrode studies recording neuronal activity. It seems that no one method is free from error, so interpretation of results must rely on the correlation of information from each. Also, the most popular experimental animal seems to have been the cat, and we cannot necessarily assume that exactly the same mechanisms exist in man.

Up until ten years ago, the theory of control, deduced from experimental surgery, supposed two independent respiratory centres in the medulla: the inspiratory centre, discharging continuously if isolated, and the expiratory centre, producing periodic inhibition of inspiratory neurons. The periodic activity of the expiratory centre was thought to be produced by the Hering-Breuer inflation reflex via the vagus nerve, and by the pneumotaxic centre, thought to act as a pacemaker through its periodic spontaneous discharge.

This older view has recently been modified.

a) *Pneumotaxic Centre*

The pneumotaxic centre, located in the upper pons, has been found to contain neurons discharging during inspiration, and inspiratory-expiratory phase-spanning neurons.[1] Stimulation of this area in the cat produces more rapid and shallow respiration, and a shift to the inspiratory phase of the breathing cycle. Transection of the upper pons produces slower and deeper breathing, and if vagotomy is also carried out, apneusis (cessation of breathing in the inspiratory phase) ensues.

It has recently been shown[2] that the pneumotaxic centre is not inherently rhythmic, but that its rhythmicity is probably dependent on respiratory activity of other regions of the brain stem, and, therefore, it cannot be considered a pacemaker. This centre is now thought to alter the tonic activity of the apneustic centre in the pons (along with the vagus), and possibly to act as a negative feed-back centre; i.e., impulses from inspiratory neurons ascend to the pneumotaxic centre, which discharges to inhibit inspiration when a certain level has been reached.[3]

b) *Apneustic Centre*

Pitts[4] and Stella[5] considered that apneusis was due to the medullary inspiratory centre, which they thought to be tonically active in the absence of inhibitory influences from the pneumotaxic centre and the vagus nerves. However, Wang *et al.*[6] showed that total removal of the pons in the vagotomized cat abolished apneusis, and produced instead gasping and poorly coordinated but rhythmic respiration. Therefore, apneusis must originate in the pons, and evidence indicates a centre in the middle and caudal pons.

Inspiratory neurons discharge throughout inspiration and expiratory neurons throughout expiration. Studies of the apneustic centre in the pons of the cat have demonstrated the presence of phase-spanning neurons, which discharge from mid-inspiration to mid-expiration (or vice versa), and it is suggested that these neurons build up an inhibitory sate during one phase of the respiratory cycle and promote thhe transition to the other phase. Although respiratory rhythm occurs without the apneustic centre, these pontine phase-spanning neurons appear necessary for normal respiration.[1 3]

c) *Medullary Centres*

Pitts[7], who carried out the first extensive and systematic study of the medulla of the cat by electrical stimulation, located an inspiratory centre in the ventral reticular formation, and an expiratory centre dorsad and cephalad to the former, although there was some intermingling of neurons. Some evidence suggests that distinct segregation of the neurons into anatomical centres does not exist.

Origin of Respiratory Rhythm

Wang[6] and Hoff and Breckenridge[8] observed rhythmic breathing in medullary animals without the influences of the pons or vagus nerves, and therefore concluded that respiratotry rhyhmicity resides in the medulla.

Salmoiraghi, Burns and Baumgarten,[9 10 11 12] who have extensively studied the medullary respiratory neuronal discharge in the cat, found that halting respiration by a cut below the medulla did not affect the regular bursts of discharge of the neurons. If these animals were maintained by artificial respiration, the respiratory neurons showed a rhythm of regular bursts quite independent of the frequency of artificial ventilation, even if the amplitude of forced chest movement was quite large. This would seem to discount the theory that vagal impulses could set the respiratory rhythm, and they concluded that afferent vagal activity can only *modify* the behaviour of respiratory cells.

Thus, in the absence of vagal and pneumotaxic mechanisms in the production of rhythmical breathing, could the medullary centres themselves discharge rhythmically? By sampling inspiratory and expiratory neurons for temporal patterns of discharge, Salmoiraghi, Baumgarten and Burns provided an estimate of the probability that each type of neuron will fire at various times during the respiratory cycle. They found that the greater the net activity of inspiratory neurons, the lesser the activity of expiratory neurons, and through the whole respiratory cycle, of the probabilities of discharge of expiratory and inspiratory neurons is constant. This would suggest linking of the two systems of neurons by reciprocal innervation.

Recording intracellular potentials from respiratory neurons in the cat[12] has shown that the neurons are progressively depolarized during activity and repolarized during quiescence. During each burst of activity (of inspiratory neurons during inspiration and expiratory neurons during expiration) repeated spike discharges occur, but the membrane potential level from which spikes originate becomes less negative as the burst of action potentials progresses, and finally the membrane potential returns to its "pre-firing" level. This progressive decrease in negativity of the "firing-level" would tend to self-limit the duration of each burst.

Hyperpolarization of expiratory neurons during inspiration was also recorded, and this would support the idea of reciprocal inhibition of one system of neurons by the other.

The neurons in each system are closely related synaptically, so that excitation of a small part of one centre could lead to activity of the whole centre. There is also evidence for self-reexcitation within the system. In these ways the discharge can be coordinated, and the entire system of expiratory or inspiratory neurons can be expected to discharge at approximately the same time.

The excitability of respiratory neurons is dependent on the activity of neighbouring neurons, respiratory or not, and on all the excitatory and inhibitory impulses (including chemical) converging on the brain stem. It can be presumed that the excitatory influences would slowly depolarize the neuron until the membrane potential reached the level for a spike potential, and that inhibitory impulses would hyperpolarize the membrane.

Although, by this concept, the medulla is intrinsically rhythmic, it is not necessary to suppose that non-medullary factors cannot alter the pattern of discharge. For example, it is thought that impulses from the pneumotaxic centre and from vagal afferents act on the apneustic centre, which then acts on the medullary centre in the generation of the normal breathing pattern.

2. *CHEMICAL CONTROL*

Chemical regulation of respiration is effected by the partial pressures of CO_2 and O_2 and the pH of the blood, acting directly on the respiratory centres or reflexly via chemoreceptors. Considering the effect of the total chemical stimulus, any change in the ventilatory level will cause a shift of the chemical stimulus, tending to restore the previous rate; or, a change in metabolic rate will cause a chemical change which will bring about an appropriate change in ventilation and, thus, also restore to normal the chemical stimulus. Thus, the interaction of metabolism, ventilation and blood chemistry may be considered either as a system for stabilizing the arterial gas tensions, or as a mechanism tending to maintain ventilation proportional to metabolism.[13]

a) *Effect of pCO_2*

Decreased pCO_2 causes an inhibition of breathing and increased pCO_2 acts as a respiratory stimulant. If CO_2 is added to inspired air, the curve of respiratory minute volume vs. alveolar pCO_2 rises steeply in the range of 5 - 10% alveolar pCO_2, flattens out from 10 - 20%, and starts to fall at 20% (toxic depression). The respiratory response to CO_2 is much greater than to hypoxia or acidosis, but increased CO_2 alone can not elicit the maximal breathing response, as may be seen in severe exercise.

Cutting all afferent nerves to the respiratory centres does not affect the response to hypercapnia, so the effect of CO_2 must be central. There is some conflict as to whether respiratory neurons are themselves chemosensitive, or if there are distinct chemoreceptors in the brain-stem.

b) *Effects of pO_2 and pH*

Decreased pO_2 and pH of arterial blood act reflexly via the chemoreceptors in the carotid and aortic bodies to stimulate respiration. It is thought that they play a minor role in the regulation of normal breathing, the main effect being the effect of pCO_2 centrally.

c) *Multifactor theories*

None of the chemical stimuli can be considered independently, however, and Gray[14] has proposed a *multifactor* theory, concluding that steady-state ventilation changes in direct proportion to changes in arterial pCO_2 and pH, and that the simultaneous effects of the two are algebraically additive. The interaction between pO_2 and pCO_2 or pH are multiplicative.

Other investigators have explored the idea that the common denominator of chemical control might be intracellular $[H^+]$, which could be affected by changes in arterial pCO_2, pO_2 and pH, and could act both centrally and on the chemoreceptors.[15]

3. *REFLEX CONTROL*

a) *Chemoreceptors*

Afferent impulses travel up cranial nerves IX and X (see above).

b) *Hering - Breuer inflation reflex*

Inflation of the lungs of an animal produces relaxation of the diaphragm and terminates inspiration. The reflex is abolished by vagotomy and breathing becomes slower and deeper. It is postulated that *pulmonary stretch receptors* located in the tracheo-bronchial tree, and concentrated at the points of branching, are responsible for the reflex. According to most conventional accounts of the control of respiration, these receptors produce discharges along the afferent fibres of the vagus when stimulated by stretch to inhibit inspiration, and are, thus, an important factor in the production of rhythmic breathing.[16]

Recently, however, it has been found that this reflex is weak in man![17]

Several investigators have found that at any alveolar ventilation rate there is an optimal frequency of breathing and a corresponding tidal volume at which the mean force of respiratory muscle contraction, or the mechanical work of breathing, is minimal. A change in the mechanical properties of the chest or lung may produce a new optimal pattern. It is possible that the pulmonary stretch receptors, via the vagus, could be instrumental in signalling changes in the mechanical properties of the lungs or chest and, so, alter the breathing pattern to produce a different optimal frequency.[18]

c) *Blood pressure*

Increased arterial blood pressure stimulates respiration reflexly via the carotid sinus nerves, but it is unknown whether this is due to the baroreceptor, chemoreceptor, or both.[16]

d) *Pulmonary vascular bed*

Increase in pulmonary arterial pressure, or more effectively, increase in pulmonary venous pressure alone, produces reflex apnea followed by tachypnea. The reflex is abolished by vagotomy.[16]

e) *Temperature*

Hyperpnea is the usual response to increase in skin temperature, and the effect is presumed to be reflex in nature.[18]

f) *Irritant Reflexes*

Chemical or mechanical irritation of the lower respiratory tract produces a cough. The afferent impulses of the reflex travel mainly in the vagus, with a few in the sympathetics.

g) *Reflexes from muscles, tendons and joints*

i) Limbs

Afferent impulses from the muscles, tendons and joints of the limbs are generally implicated in the increased respiration during exercise.

ii) Chest wall

Inspiratory muscles are opposed by two types of mechanical loads, the elastic load (measured as compliance), comprised of the elastic properties of the lungs and the surface tension of the fluids lining the airways, and non-elastic loads (measured as resistance), comprised mainly of the frictional resistance of the respiratory passages to airflow. Campbell and Howell[19,20] in studies of respiratory sensation, found that normal subjects detected the addition of external elastic and non-elastic loads which were greater than 20% of the normal loading of the respiratory muscles. In disease states, the increased mechanical load is often 60 - 70% of normal. They suggest that two distinct types of information, one concerning tension (or pressure) and the other length (or volume) form the sensation, and that added loads are detected by the disturbance they cause in the relation between the tensions developed in the inspiratory muscles and the resultant changes in the dimensions of the chest (i.e., the *length/tension inappropriateness*).

These same investigators found that the response to added loads was an increased force of contraction of the respiratory muscles, so that tidal volume was frequently maintained despite a considerable increase in the work load. The response is too rapid to be due to an alteration in blood gas tensions, and animal experiments eliminated the possibility of vagal afferent impulses being responsible. The response was shown to be reflex, with the stimulus being the altered relationship between the degree of shortening and the tension developed by the inspiratory muscles.

The receptors implicated are the muscle spindle and tendon and joint receptors in the chest wall. The muscle spindle, consisting of a sensory and a motor component (intrafusal muscle fibre), is in parallel with the main (extrafusal) muscle fibres. The discharge of

the sensory component is increased by stretch, and, therefore, the discharge is decreased by contraction of the main muscle fibre (controlled by the alpha system) and increased by contraction of the intrafusal muscle fibre (controlled by the gamma system). The sensory discharge is, thus, dependent on the alignment of the intra- and extrafusal muscle fibres, and can signal any misalignment during contraction (i.e., any difference between the two in the degree of shortening).

CONCLUSION

Taking Campbell and Howell's proprioceptive theory into account, the following scheme for the control of respiration may be advanced. One could think of respiration in terms of a *demand* by the central mechanism for a certain alveolar ventilation, and the *effort* required of the respiratory muscles to meet this demand. The respiratory centres could be thought to consist of two functional parts: a computer, and a servo-mechanism.[13] The input into the computer would comprise chemical factors, nervous influences (both from the periphery and from higher centres), and information about the mechanical state of the lungs (probably via the vagus). The output of the computer and the input of the servo-mechanism is correlated to produce a *demand* for the required ventilation; i.e., for a certain frequency and tidal volume. This demand passes down the alpha-neurons to the inspiratory muscles, which then contract, producing an expansion of the thoracic cage and lungs by an amount depending on the tension exerted and the elastic and resistive loads of the thoracic cage and lungs. The output of the servo-mechanism (gamma system) could then serve to adjust the (alpha-) motor-nerve activity to ensure the achievement of the set *demand*, so that despite changing mechanical conditions, tidal volume and alveolar ventilation could be stabilized without a resetting of the primary demand (i.e., without a change in blood gas tensions).[20]

B. The Aetiology of Dyspnea

DEFINITION

Many of the problems of defining dyspnea have arisen because it has been impossible to equate the pathophysiological conditions which cause dyspnea with upsets in the normal regulation of respiration. Dorland's Medical Dictionary defines dyspnea as *difficult or laboured breathing*.[21] However, in common usage it is taken to mean abnormal breathlessness or short-windedness with a pathological basis. Such restricted usage is probably unjustified as anyone who has just run a mile will tell you. Perhaps, therefore, it is best to define dyspnea as the *subjective* awareness of respiratory distress.[22] Dyspnea is usually a form of breathlessness that is distressing or unusual because of the circumstance under which it develops or becausc of the strange sensation present. It may or may not be associated with signs of laboured breathing or respiratory distress. Dyspnea may be inspiratory, expiratory, paroxysmal or sighing. Dyspneic breathing can be shallow, deep, regular or irregular. Dyspnea is associated with an awareness which may vary from mild discomfort to panic. Both its interpretation and description are affected greatly by not only the organic disease underlying it, but also by psychogenic factors which may be superimposed. Dyspnea, a subjective phenomenon, should not be confused with objective terms often used to describe respiration; e.g., polypnea (rapid), tachypnea (rapid and shallow), hyperpnea (increased depth) and oligopnea (slow or small volume breathing).[23]

Previous reference has been made to the muscle spindle, which is ideally set up to be a servo system for measuring, interpreting and responding to alteration in lung compliance and resistance. Campbell and Howell suggest that in normal respiration there is a balance between ventilatory *demand*, and the *effort* of breathing to meet this demand.[19] Asynchrony of the demand and effort (*length/tension inappropriateness*) may be the reason that breathing, normally unconscious, becomes a conscious sensation and eventually results in dyspnea. As with all theories, there is a danger of over-simplification. However, the Campbell and Howell theory of length/tension inappropriateness is a particularly useful model, for it does explain, in most instances, the actiology and sensation of dyspnea.

THE PATHOPHYSIOLOGY AND CAUSES OF DYSPNEA

The causes of dyspnea are legion. They range from obesity, hypoxia of altitude, and thyrotoxicosis to neurosis, and from muscular disease to pulmonary oedema. Dyspnea may be classified as in Table 1.

Table 1. CAUSES OF DYSPNEA

A. Respiratory
- **1. Ventilation**
  - **a) constriction or obstruction of upper air passages**
  - **b) glottic and laryngeal obstruction**
  - **c) lower air passage obstruction; e.g., asthma**
- **2. Diffusion and Perfusion Defects**
- **3. Parenchymal**
  - **a) alveolar; e.g., pneumonia, bullae and cysts**
  - **b) interstitial; e.g., fibrosis, viral pneumonia**
- **4. Pleural; e.g., pain, effusion**
- **5. Diaphragm; e.g., phrenic nerve paralysis**
- **6. Chest Wall; e.g., myasthenia gravis, Parkinson's Disease, pain**
- **7. Spine; e.g., kyphosis**

B. Disturbances in Circulation; e.g., pulmonary oedema

C. Haematological; e.g., anaemia, leukaemia

D. Metabolic and Endocrine; e.g., thyrotoxicosis, obesity

E. Cerebral Disease; e.g., poisoning

F. Degenerative; e.g., senescence

G. Psychogenic Disturbances

H. Normal Activities; e.g., sports, pregnancy, high altitude travel, SCUBA diving.

Many of the causes of dyspnea have more than one basis, and cannot always be explained in terms of demand and effort, as will be apparent from the following discussion of the pathomechanics of some of the common causes of dyspnea.

1. *Pneumonia*

Clinically, pneumonia often presents as fever and dypsnea. For simplicity, pneumonias may be divided into massive (lobar), disseminated (broncho-pneumonia) and interstitial (pneumonitis).

In massive pneumonia there is bronchial inflammation with an increase in secretions, oedema and irritation. These factors may stimulate cough and, hence, induce bronchospasm and further luminal narrowing. The net effect of bronchial constriction is to increase the work of the expiratory phase of respiration. In addition, there are large areas of serum- and cell-filled alveoli, which are still perfused with blood and, hence, function as arterio-venous shunts, returning un-oxygenated, slightly acidic blood to the systemic circulation. In areas where there is still partial gas exchange, CO_2, being twenty-one times more diffusible,[21] will diffuse outwards, but O_2 will not enter. The net effect is an arterio-venous shunt. The ultimate result of this arterio-venous mixing is an increase in pCO_2, and decrease in pO_2 and pH. These chemical changes will alter the demand and stimulate an increase in rate and depth of respiration. This demand is augmented by the increase in temperature and metabolic rate in pneumonia. The effect of increased rate of respiration in the face of coexisting bronchial narrowing is to further increase the effort of breathing. With consolidation in lobar pneumonia, the lung resists change in inspiration and expiration; that is, compliance decreases. With this pronounced increase in work due to both elastic and non-elastic factors, the oxygen requirements of the respiratory muscles are increased. If the patient is extremely ill, the capacity of his respiratory muscles and heart to meet the demand for ventilation may be inadequate, and the degree of dyspnea may be severe. With the passage of time there is a tendency for circulation to shunt away from the affected area to uninvolved portions of the lung. This may give rise to apparent lessening of symptoms without resolution of the pneumonic process.

In the case of disseminated pneumonia, the same basic pathophysiology causes dyspnea, but there are more areas of partial involvement and the bronchial component is much increased. This bronchial narrowing may produce alveolar hypoventilation in areas not directly involved by the pneumonia.

In interstitial pneumonitis (e.g., viral pneumonia, farmer's lung), the major pathology is interstitial inflammation with only minor alveolar and bronchiolar involvement. This results in a profound loss in compliance. The pressure necessary to expand the lung increases as the square of the lung volume, and, therefore, expansion is often the first problem in interstitial disease. In order to reduce elastic work to a minimum the patient will start to breathe rapidly. When he can no longer achieve the effort (work) to meet the demand for O_2, true dyspnea will develop. In addition to a decrease in compliance, a degree of alveolar-capillary block is induced (i.e., CO_2 diffuses out more readily than O_2 enters). In viral pneumonitis with bronchiolitis, ventilation may be interfered with, and cough and bronchospasm may be present. The toxicity and weakness associated with viral disease may limit the patient's capacity to respond to the demand for ventilation.

2. *Pulmonary Oedema and Left Heart Failure*

It is well recognized that dyspnea (orthopnea, paroxysmal nocturnal dyspnea) is an early symptom of left heart failure. In a normal individual, additional oxygen requirement is met by an increased cardiac output. Patients with left heart failure have a limited capacity to increase their cardiac output, and can only gain additional oxygen by a greater extraction of oxygen by tissues. The result of this is to increase the arterial-venous oxygen difference, decrease the availability of oxygen for the respiratory muscles and stimulate the respiratory centre. This may produce dyspnea. In early congestive heart failure, pulmonary congestion is not important, but rather it is the decrease in cardiac output and resultant muscular fatigue that causes the patient to experience his first symptoms (cf., mitral and aortic stenosis).

In late left heart failure, pulmonary congestion is the main cause of cardiac dyspnea. There is an increase in pulmonary capillary and venous pressure, which may produce interstitial oedema, encroachment on the alveolar spaces, and frank oedema fluid in the alveoli. Respiration is disturbed by a decreased compliance and impaired oxygen diffusion. Increased airway resistance due to oedema and bronchospasm (viz., *cardiac asthma*) increases the expiratory load. Efforts to minimize work take the form of the familiar rapid shallow respirations. This tachypnea in turn may increase the dead space ventilation, but at least the patient at first usually maintains a normal arterial pO_2. The role of the vagus in congestive failure, while established in animals, is not clearly defined in man. Distension of the pulmonary vessels (Churchill-Cope reflex) and alveolar distension (Hering-Breuer reflex) can both, via afferent vagal impulses to the respiratory centre, give rise to rapid shallow breathing.

3. *Anaemia*

Many explanations have been advanced to explain the dyspnea, fatigue and weakness of anaemia. It has been postulated that the fatigue and dyspnea are secondary to heart failure due to cardiac muscle hypoxia, cardiac hypertrophy, fatty infiltration and coronary artery disease as seen in chronic or severe anaemias. A

low arterial pO_2 may stimulate the carotid body, the brain and respiratory centre, and alter the demand. In addition, a low pO_2 will increase the anaerobic glycolysis of muscle, and thereby increase the production of lactic acid, which is thought to have a direct stimulating effect on the respiratory centre. Again the effect will be to stimulate respiration and produce dyspnea. Other factors which have been implicated are a decrease in cardiac reserve for exercise, the decreased availability of the haemoglobin buffer system for CO_2, and a decrease in carbonic anhydrase. Some authors have suggested that there is an upset in alveolar-capillary diffusion in anaemia.[25]

4. *Thyrotoxicosis*

Neglecting those cases where a goitre directly compresses the trachea, producing dyspnea, there have been a number of explanations advanced to explain the dyspnea occurring in hyperthyroidism. These may be summarized as follows. There is a thyrotoxic myopathy which severely limits the individual's capacity to increase his work of respiration. Compliance decreases due to pulmonary congestion and partial oedema. There is an abnormally high production of CO_2 and heat during exercise which stimulate the respiratory *demand* centre. The respiratory centre appears to be directly stimulated by thyroid hormone and by the higher arterio-venous oxygen gradient arising from the increased utilization of oxygen by the tissues.

5. *Dyspnea in the Geriatric Patient*

There is a tendency to attribute dyspnea in the older patient to respiratory or cardiovascular pathology. This in fact may be unjustified, for there are many reasons why the geriatric patient may experience dyspnea without having primary lung or heart pathology. Respiratory excursions and distensibility are reduced because of calcification or limitation in movement of costochondral and costoverterbral joints and loss of elasticity of the thoracic ligaments. The patients often are weaker and have a decreased resilience of their tissues. In the lungs there may be alveolar atrophy and thinning, loss of elasticity, bronchial sclerosis and calcification (further decreasing elasticity). The primary result of these is to increase the effort or work of breathing. Intimal and medial sclerosis of pulmonary vessels renders the vessels arteriosclerotic and decreases the adaptive capacity of the pulmonary circulation. The central portion of the diaphragm becomes more fibrotic and rigid and there is a loss of diaphragmatic muscle tone. These physical changes are augmented by a decreased metabolic rate with age, coupled with a decreased oxygen uptake. In addition, it has been shown that in geriatric patients, the lung residual volume increases, and that there is a tendency to fluid retention which will predispose to bronchospasm.

6. *Emphysema and Dyspnea*

Of all lung diseases, emphysema and bronchitis constitute theh commonest cause or contributing cause of dyspnea. Of the types of emphysema, obstructive types (panacinar and centrilobular) are the most common. Clinically, these are aptly named, for it is the obstructive element of emphysema which first causes dyspnea because of increased work (due to obstruction) and concomitant decrease in ventilatory capacity.[26] It may be well to point out that the clinical appearance of the patient is quite unreliable in establishing the diagnosis, but that the patient must experience dyspnea on exercise and have evidence of obstruction, increased residual volume, and uneven distribution of gases by pulmonary function tests (e.g., maximum expiratory flow rate less than 100 l./min., nitrogen washout test or pure O_2 inhalation). The obstructive increase in resistance to airflow is due to allergic or inflammatory oedema of the mucosa of small bronchi and bronchioles, the presence of retained viscid secretions, loss of normal elastic recoil of lung parenchyma, and, finally, bronchospasm associated with cough. The normal expiratory closure of bronchioles is accented in this disease and there may be air trapping with over-inflation. This trapping is uneven and results in unequal distribution, perfusion and obstruction to airflow. In poorly ventilated areas venous admixing may occur. A decrease in compliance tends to occur at first only with exercise, but eventually will contribute significantly to the work of breathing. Dyspnea results from the increasing work (*effort*) of breathing and decreasing ventilatory capacity in the face of increased ventilatory demands. In severe disease compensatory hyperventilation becomes impossible and alveolar hypoventilation ensues with a decrease in pO_2, increase in pCO_2 and respiratory acidosis. The respiratory centre appears to be rendered insensitive to CO_2 and is driven by oxygen demand. Some recent evidence indicates that only at a pH above 7.35 is respiration depressed by oxygen administration.[27] The secondary polycythaemia which may occur in emphysema is a mixed blessing, for while partially increasing the oxygen carrying capacity of the blood, there is an increase in the viscosity of the blood, which will increase the work of the heart and contribute to vascular thrombosis and cor pulmonale. Further limitation to effective respiration comes from the lowering and decreased excursion of the diaphragm.

7. *Psychogenic Dyspnea*

Psychogenic dyspnea is one of the commonest symptoms encountered in clinical medicine and deserves special mention because it may *simulate* organic disease (primary psychogenic dyspnea), or it may be *superimposed* on true organic disease (secondary psychogenic dyspnea). Sparer and Davis[28] suggest that basic to the understanding of psychogenic dyspnea is the psychoneurotic condition of anxiety. The symptoms and signs of anxiety are primarily mediated through the limbic,

hypothalamic, pituitary, parasympathetic and sympathetic networks, and usually take the form of apparent autonomic imbalance (autonomic dystonia). The psychiatric concomitants and mental mechanism of the anxiety reaction will not be discussed, but are of great importance in understanding the patient.

The *diagnosis* of psychogenic dyspnea is *not made by excluding organic disease*. It is a diagnosis made by positive clinical findings in the history, physical examination, laboratory investigation and assessment of the patient's personality structure. By careful and tactful listening and interrogation it should be possible to obtain an accurate description of the dyspnea. In anxiety states, shortness of breath often occurs *after* exercise, or it may be described as the inability to take a deep breath or to "fill the lungs". On physical examination, an effort should be made to screen for organic disease; however, a diagnosis of psychogenic dyspnea is suggested by a discrepancy in symptoms and signs, and by evidence of autonomic imbalance in other systems (e.g., sweating, sighing, tachycardia, tremors, apprehension, etc.). Laboratory investigation may range from the minimal, such as reproduction of the patient's symptoms in the hyperventilation syndrome, to extensive utilization of pulmonary and cardiac function tests. Anxious patients often have difficulty in performing these tests because they cannot cooperate fully, the test often being upset by irregular breathing, restlessness or sighing. The psychological assessment of the patient is often the most fruitful part of the examination. *Even the demonstration of a real organic lesion does not rule out the possibility that both psychogenic and organic disease are present.*

Very naturally, organic chest or cardiac disease may give rise to much justified anxiety. Often, however, these patients will experience a degree of dypsnea that far exceeds the degree of limitation imposed by the disease (secondary psychogenic dyspnea).

Two of the more commonly recognized conditions which may cause psychogenic dyspnea are the hyperventilation syndrome and the effort syndrome (neurocirculatory asthenia). The hyperventilation syndrome is an acute episode associated with acute anxiety, typically in young females, often preceded by the sense of suffocation and followed by an increase in the rate and depth of breathing, perioral and peripheral paraesthesia, lightheadedness, blurred vision, dulling of the sensorium, fainting and eventually tetany. Biochemically, with hyperventilation, the pCO_2 may fall to less than 20 mm. Hg and the pO_2 and pH increase. Shifts in potassium, phosphorus and calcium, due to the decrease in pCO_2 and alkaline pH, may explain the presence of carpopedal spasm. There may be electrocardiographic changes in the form of lowered T waves, depression of the ST segment and prolongation of the QT interval. When accompanied by chest pain the picture must be clearly distinguished from acute coronary insufficiency. The effort syndrome is a chronic hyperventilation syndrome and results from chronic anxiety. Typically such patients suffer from chronic fatigue and have dysnea, palpitations, precordial pain, giddiness or faintness with the slightest exertion.

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An Introduction to Pulmonary Function Tests

F. Tan 6T9

Pulmonary function tests are assuming an increasing importance in medicine, in increasing understanding of diseases of the lung and in the management of such diseases. It is the purpose of this paper to discuss the indications for these tests, the types of tests available, their methodology, their interpretation in terms of altered physiology and possible ethiological factors, and their limitations.

INDICATIONS

Pulmonary function tests can be applied as a guide to the most suitable treatment for a patient, for the evaluation of new therapeutic agents, as a guide to the progress of diseases where the respiratory muscles are dangerously weakened, in the preoperative assessment for thoracic or other major surgery, to assist in diagnosis, to obtain a better understanding of the underlying functional problems of patients complaining of dyspnoea, and as an objective measure of disability, particularly in medico-legal and compensation cases.

TYPES OF TESTS

Five categories of respiratory functions that can be measured are:

1. Ventilation—the mass displacement of air between the outside atmosphere and the interior of the lungs;

2. Gas Mixing—distribution of the inhaled gas to the alveoli;

3. Diffusing capacity—diffusion of oxygen and carbon dioxide across the alveolar-capillary membrane;

4. The pulmonary circulation;

5. The work and mechanics of breathing.

METHODOLOGY

1. *Ventilation*

Some abnormality of ventilation is found in almost all patients with pulmonary insufficiency. The three most important tests of ventilation are:

(1) Timed vital capacity;
(2) Maximum mid-expiratory flow rate;
(3) Maximum voluntary ventilation.

Timed vital capacity:

When one measures *forced vital capacity* (the volume of air that can be expired after a maximal inspiration, or the volume inspired after a maximal expiration), the patient is instructed to take a maximum inspiration as rapidly and forcefully as possible through a spirometer. In this way the form of the inspiratory and expiratory curves can be seen, and the total vital capacity measured. The value obtained for the patient is compared with the average normal values calculated on the basis of sex, height and weight and expressed as a percentage thereof.

The percentage of vital capacity forcibly expired in 1, 2 and 3 seconds may be measured, as the *timed vital capacity*. The *forced expiratory volume* is the percentage recorded for one second. This provides an excellent objective assessment for patients suffering from primarily obstructive lesions.

Maximum mid-expiratory flow rate:

This is the most sensitive test for obstruction. A tracing of volume expired against time in seconds is made. The maximum volume of air expired during an exhalation is v litres. The positions on the tracing corresponding to ¼ v litres and ¾ v litres are marked and joined by a line. The gradient of this line indicates the *mid-expiratory flow rate*. A value of less than 3 litres per second indicates the presence of an obstruction.

Maximum voluntary ventilation:

The *maximum voluntary ventilation* is the maximal volume of gas that a patient is capable of breathing voluntarily in one minute. The test is usually carried out over a period of 15 seconds and the result that would ensue for a minute calculated from this. The standard normal is calculated in a similar manner to that for vital capacity. On this basis, the patient's values are expressed as a percentage of the normal. This value is an accurate estimation of the patient's ventilatory disability.

2. *Gas Mixing*

This is of less clinical importance than the other tests. However, it may be measured. It is the nitrogen content of the alveolar air (collected at the end of expiration) (i) after a single breath of oxygen, or (ii) after breathing oxygen for seven minutes (the nitrogen washout test). Alternatively, one can study the evenness by which helium enters the lung (helium dilution test).

3. *Diffusing capacity*

The tests used to estimate gas exchange across the alveolar-capillary membrane are:

(1) Oxygen saturation and tension of arterial blood —(a) at rest, and (b) during exercise;
(2) Carbon dioxide tension of arterial blood;
(3) Carbon dioxide combining power of venous blood;
(4) Alveolar-capillary membrane and diffusion capacity.

Oxygen Saturation and Tension of Arterial Blood:

A sample of blood is taken by arterial puncture or by external ear oximetry. These samples may be analyzed for oxygen content, which is expressed as *per cent saturation*. Alternatively, one may measure the oxygen tension of the blood. This is more sensitve for measuring slight degrees of anoxia but technically more difficult.

Samples may be taken both at rest, and after exercise. Arterial oxygen saturation in normal subjects should decrease only minimally after exercise.

Arterial oxygen saturation is decreased not only when diffusion capacity is impaired but also when any of the other pulmonary functions is impaired. Accordingly oxygen saturation is a measure of overall pulmonary function.

Carbon Dioxide Tension of Arterial Blood:

Arterial blood may be analysed for carbon dioxide content or tension. The latter is technically more difficult but is a more sensitive index of abnormalities. In contrast to oxygen deficit, carbon dioxide excess does not occur when there is a defect in diffusion because carbon dioxide diffuses twenty times as readily as oxygen across the alveolar membrane. Accordingly, respiratory acidosis (a raised carbon dioxide content or combining power and a low blood pH) requires hypoventilation of the whole lung or a major part of it. In diffusion defects carbon dioxide content is usually within normal limits.

Arterial Carbon Dioxide Tension
(Rebreathing technique)

The p CO_2 of alveolar air can be equilibrated with that in an anaesthetic bag and the p CO_2 of the air in the bag measured. This gives an index of the p CO_2 in alveolar air. The p CO_2 of mixed venous blood can be assumed to be equal to that of alveolar air.

The p CO_2 of arterial blood is assumed to be 6 mm. Hg less than that of venous blood. Accordingly an estimate of arterial p CO_2 may be obtained.

Carbon Dioxide Combining Power of Venous Blood:

This is a relatively poor index of carbon dioxide elimination.

Alveolar-Capillary Membrane and Diffusion Capacity:

The diffusion capacity may be measured by the use of special apparatus and carbon monoxide. The carbon monoxide concentration in inspired air, end-tidal air ("alveolar air"), and mixed (total) expired air is measured. Simultaneously, the respiratory rate, tidal volume and minute volume are recorded. Then, using formulae devised by Bates, one may calculate the amount of carbon monoxide that diffused across the alveolar-capillary membrane and was absorbed by the patient, per minute at a given partial pressure of the gas. Measured in this way, the diffusing capacity of carbon monoxide should be great than 12 ml. per minute per mm. Hg. A value less than this indicates a diffusion defect or alveolar-capillary block.[2]

4. *The Pulmonary Circulation*

The pressures in the pulmonary circulation may be measured by catheterization. Furthermore the relationships of pulmonary circulation to alveolar ventilation may be investigated, but these tests are not done routinely.

5. *The Work of Breathing*

It is possible to measure the mechanical work in breathing and the mechanical factors involved (forces required to overcome elastic and non-elastic resistance; and the forces required to overcome resistance to air flow). However, such measurements are used mainly for research purposes.

INTERPRETATIONS OF THE TESTS

The three main types of pulmonary insufficiency are:

1. Restrictive ventilatory insufficiency;
2. Obstructive ventilatory insufficiency;
3. Diffusion defect or alveolar-capillary block.

More than one of these defects may occur in the same individual.

Findings in Each Type of Defect

1. *Restrictive ventilatory insufficiency*

In this case, the vital capacity and other lung volumes are usually reduced. The maximum breathing capacity will reflect the amount of dyspnoea; *the vital capacity is much more reduced than the maximum breathing capacity.*

The intra-pulmonary gas mixing and diffusing capacity are usually normal. If the deficit is severe the arterial oxygen saturation will fall and the carbon dioxide content will rise, especially on exericse.

2. *Obstructive ventilatory insufficiency*

The chief difficulty here is obstruction to air flow. The vital capacity is normal or slightly to moderately reduced. The residual volume rises relative to the vital capacity. The forced expiratory volume and the maximum mid-expiratory flow rate fall due to the obstruc-

tion which may be greatest during expiration. During the measurement of maximum breathing capacity the individual may breathe rapidly or deeply but not both. Thus, *maximum breathing capacity is much more reduced than vital capacity*. Moreover, during rapid breathing, the patient is unable to expire a breath fully before the next inspiration is due, so that more and more air is trapped in his lungs until he is breathing rapidly and shallowly in the full inspiratory position.

In addition, gas mixing is usually abnormal. Diffusion is normal except in some severe cases of emphysema where there is a decrease in the surface area for diffusion due to a marked decrease in the number of functioning alveoli in contact with functioning capillaries. The arterial oxygen and carbon dioxide again reflect the pulmonary function.

3. *Diffusion defect or alveolar-capillary block*

This is an uncommon condition in which there is sufficient thickening of the alveolar capillary membrane to impair the diffusion of oxygen.

The patient may be cyanotic and complain of dyspnoea on exertion. The ventilatory function is normal or slightly decreased. Intrapulmonary gas mixing is normal or slightly impaired. However, the arterial oxygen saturation may be normal or low, and falls on exercise. Since the diffusion of carbon dioxide is unaffected by thickening of the alveolar-capillary membrane and the patient tends to hyperventilate at rest, the carbon dioxide content of the arterial blood is low.

Intracardiac or intrapulmonary veno-arterial shunt will also produce a severe fall of arterial oxygen saturation with little rise in carbon dioxide in spite of normal ventilation. However, in this case the arterial oxygen saturation will remain low even when 100% oxygen is breathed because the blood passing through the shunt is not exposed to the increased oxygen in the alveoli.

In contrast, in diffusion defects, breathing oxygen will always produce an arterial oxygen saturation of nearly 100%.

ETIOLOGY OF EACH TYPE OF DEFECT

1. *Restrictive ventilatory insufficiency*

The causes of this defect are:

(i) Weakness of the respiratory muscles; e.g., poliomyelitis, myasthenia gravis;

(ii) Chest wall abnormalities; e.g., kyphoscoliosis, ankylosing spondylitis, and after thoracoplasty;

(iii) Weakness or restriction of the diaphragm; e.g., phrenic paralysis, ascites, and pregnancy;

(iv) Pleural abnormalities; e.g., pleural effusion, pneumothorax, and pleural thickening;

(v) Decrease in functioning lung tissue; e.g., atelectasis, tumour, pneumonia or surgical removal of lung;

(vi) Decreased distensibility of lung tissue; e.g., pulmonary fibrosis and congestion.

II. *Obstructive ventilatory defect*

The obstruction may be:

(i) In the trachea or large bronchi; e.g., tumour;

(ii) In the smaller air passages or bronchioles; e.g., emphysema.

III. *Diffusion defect or alveolar-capillary block*

This may occur in such conditions as sarcoidosis, berylliosis, idiopathic pulmonary fibrosis, lymphangitic carcinoma of the lung and pulmonary scleroderma.

LIMITATIONS

The values in normal persons range from −20% to +20% from the mean; therefore, slight reductions of function cannot de detected. The subject usually must cooperate, so the tests cannot be done in seriously ill patients. The more sensitive tests can usually be done only with elaborate apparatus and by skilled technical staff. The tests will indicate only an alteration in physiology and will not give a pathological diagnosis.

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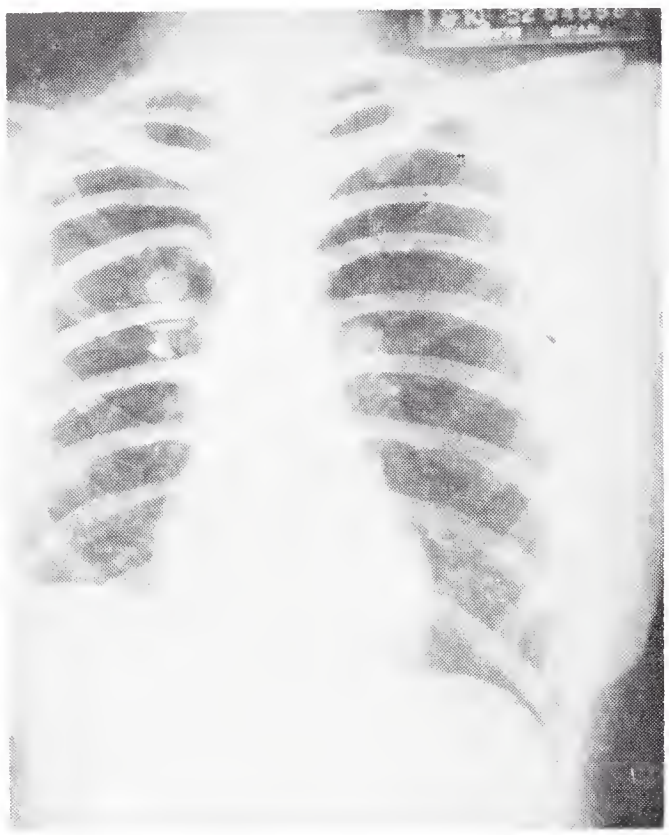
Diseases of the Lung

Answers on page 259



1. Upon admission of a patient for an unrelated condition, a routine chest X-ray revealed an isolated nodular shadow near the right hilus. What is the differential diagnosis?

2. This patient was alleged to have Boeck's sarcoid. What abnormalities of the chest may be detected in this chest film? Give a classification of pleural fluid.

3. This striking X-ray picture should suggest a differential diagnosis. Which two conditions of your differential are most likely in this patient, who has lived all his life in southern and south-western Ontario?

4. This asymptomatic male patient revealed an interesting chest lesion on a routine chest X-ray. What is the most probable site for this object? How would you manage this patient?

Pulmonary Tuberculosis

R. B. Gibb, B.A. 6T5

"Tuberculosis probably raanks among the top two or three eauses of death in the world today".[1] The World Health Organization in 1963 reported an estimated three million deaths from tuberculosis per year and fifteen million people infected with tubereulosis per year. In Canada, there were 756 deaths and 5,726 new cases during the same year. In the City of Toronto, 60 new eases per 100,000 population were reported.

The purpose of this artiele is to diseuss pulmonary tubereulosis, based on my experiences at the Toronto Hospital, Weston during the past summer.

INFECTION: The predominant mode of infection is from person to person by droplets. In other parts of the world, unpasteurized milk is a common source of infeetion. One may also become infeeted through the skin by self-innoculation as seen in laboratory workers or in butchers handling infected meat.

PREDISPOSING FACTORS: The underlying factors are soeio-eeonomic—crowded living eonditions, inadequate nutrition, aleoholism, and industry. Some combination of these factors is evident in the histories of most people who develop pulmonary tuberculosis. A good proportion of the male patients are alcoholies. Because of alcoholism, their dietary habits are poor. Miners (who develop silieosis), ehildren, female adoleseents and elderly men are also suseeptible. Certain races sueh as the Indians and Eskimos seem to be predisposed to infection.

PATHOLOGY: Any organ or tissue of the body may be involved. The gross pathology shows caseous neerosis. Mieroseopically, eharaeteristic tubereles are observed. In ehildren, a primary infection forms a Ghon lesion —a small easeous foeus in the lung with a focus in a mediastinal lymph node draining this area. The spread of infeetion is via the bronchioles and bronehi to other parts of the lung, or to the pharyngeal region from whieh the baeilli are swallowed. Hematogenous spread to any tissue of the body may oeeur.

CLASSIFICATION:[2] *Minimal* lesions include those of slight to moderate density without demonstrable cavitation. They may involve a small part of one or both lungs, but the total extent should not exceed the volume of lung present above the seeond chondroeostal junetion and the spine of the fourth or the body of the fifth thoraeic vertebrae on one side.

Moderately advanced lesions may be in one or both lungs, but the total extent should not exeeed the following limits: disseminated lesions of slight to moderate density extending throughout the total volume of one lung or the equivalent in both lungs: dense and eonfluent lesions limited to one third the volume of one lung: if cavitation is present, its total diameter must be less than four eentimeters.

Far advanced lesions are all those more extensive than moderately advanced.

Tuberculosis is further classified according to the presenting symptoms by the letters A, B, C and D, as follows: A — asymptomatic, B — slight symptoms, C — severe symptoms, and D — very severe symptoms.

SYMPTOMS: Many of the patients are discovered by routine X-ray and are asymptomatic. A change in the character of a cough or sputum is a common story. The patient often develops more frqeuent "colds", or is unable to cure a "cold", or he may present as a pneumonia. There may be hemoptysis. Other associated complaints are late afternoon fever, chills, night sweats, shortness of breath, pleuritic pain, malaise and anorexia.

SIGNS: Many patients appear normal on physical examination, but commonly the physician hears râles and rhonchi. Sweating and fever may be noted. Other findings occasionally found are inereased respiratory rate, cyanosis, deviated trachea, dullness on percussion, and amphoric breathing.

LABORATORY:

(1) *Sputum.* Three three-day pools are required on admission. The patient must be eneouraged to eough sputum up from the lungs, since some patients will expectorate saliva or post-nasal secretions from the throat. If aeid-fast bacilli are demonstrated on smear, they may represent mycobacteria tuberculosis or one of the atypieal mycobaeteria. Confirmation is made on culture or guinea-pig inoculation. Negative smears indicate that the patient has an insufficient eoneentration of baeilli or no baeilli in his sputum. One should remember that the tubercle bacillus is a relatively slow-growing bacterium. Some bacilli grow rapidly and a positive eulture may be reported in two weeks. However, some bacilli require eight weeks to grow, and this period must elapse before a report of negative is pronouneed.

What does a negative culture mean? It means that in the particular speeimen, there are no tuberele baeilli. Either the patient is unable to cough up the tubercle or he is not infected. Commonly only one or two of the three initial pools will be reported positive. Therefore, the results of the sputum may be interpreted only when the other tests are completed. There are many people admitted with a diagnosis of tuberculosis whose sputum is negative, but have aetive disease on the basis of other evidence.

One-day pools are collected monthly during the rest of the patient's hospitalization.

(2) *Gastric Lavage.* Three fasting morning samples are required if the patient is unable to raise sufficient sputum.

(3) *Hematology*. The WBC is usually not elevated. The ESR is usually elevated, but may be normal. The hemoglobin may be normal or low.

(4) *Urinalysis*. One 24-hour specimen is collected for routine and microscopic urinalysis, and for culture and sensitivity.

(5) *Other tests*. If the diagnosis is in doubt, sputum should be submitted for carcinoma cells, bacteria and fungi.

Tuberculin: There are two strengths of old tuberculin (O.T.) — number one strength containing one-twentieth mg. per 0.1 c.c. and number two strength containing one mg. per 0.1 c.c. One-tenth c.c. is given intradermally and is read 48 hours later.

Eight millimeters induration is considered positive. Actual ulceration and necrosis may occur. One of several conclusions may be drawn from a positive reading: the patient has been infected and has active or inactive disease at present; the patient has been B.C.G.-vaccinated; the patient has been infected by other mycobacteria. From this preceding knowledge and the size of the reaction, the physician's suspicions are directed accordingly. It has been observed that a B.C.G. vaccination gives a small positive reacation to No. 1 strength O.T. for one year, and a positive reaction thereafter to No. 2 strength for four to five years. A small positive reaction to No. 2 O.T. is observed in patients infected with other mycobacteria. A tuberculin reaction which is recently converted from negative to positive is overwhelming evidence of active tubercuIous disease. Whether or not the activity is harmful will be confirmed on further examination.

Radiology: There are no absolutely characteristic changes in pulmonary tuberculosis. Early one observes soft flocculent densities occupying variable areas of lung, and later cavitation with or without a fluid level. A pleural effusion may be the only finding. The site of the disease is important in suggesting the diagnosis. Tuberculosis typically is found in the apices of the upper and lower lobes posteriorly. Planograms are taken to find the site and extent of any suspected cavity.

X-rays are taken routinely on admission, at six weeks, at three months and at three-month intervals thereafter.

Differential Diagnosis: Carcinoma, pneumonia, lung abcess, sarcoidosis, chronic bronchitis, bronchiectasis, and mycosis are the main considerations.

Diagnosis: The degree of activity of tuberculosis is judged largely on roentgenographic and bacteriologic factors. On the basis of the history, physical examination and other preliminary test, a provisional diagnosis might be "Pulmonary tuberculosis minimal active A bacillary on smear". If a physician should send his patient to the sanatorium, he will receive in four weeks a brief history, diagnosis, planned course of treatment and a statement of prognosis.

Treatment: The first principle is prophylaxis — yearly chest X-rays, tuberculin testing (especially in all primary graders), and the improvement of the socio-economic status in certain areas.

Tuberculosis may be treated medically and surgically. Surgery has always been a salvage procedure where medical therapy has failed. The patient should enter hospital for the early part of treatment, thus providing the physician with some control over his care. Treatment will be considered under the following headings: Indoctrination, Public Health, Activity, Drugs, Rehabilitation and Post-Sanatorium Care.

Indoctrination: The patient is instructed to turn his head away from other people on coughing. He must also cover his mouth and nose with tissues. A general explanation of the disease and the proposed treatment are given. The patient must realize the severity of his illness and the necessity of taking the medication properly.

Isolation from children is necessary. Kissing and using the same utensils should not be continued, if the patient remains at home.

Public Health: The public health department must be notified about this case. All contacts must be located for tuberculin testing and chest X-rays. Notification to the public health department of your intent to discharge a patient should be given. They inquire about the patient's proposed living quarters, and give their approval.

Activity: Bed rest is a controversial factor today in antituberculosis therapy. It is believed that bed rest is important for the first four to six weeks until a second X-ray is taken and the progress is assessed. Increased ambulation may be instituted then. Many authorities obtain good results on ambulatory treatment.

Drugs: The most popular drugs are streptomycin (Sm), paraaminosalicylic acid (PAS) and isoniazid (INH). INH is the best and most effective antituberculosis drug. Full doses of INH (300 mg.) and PAS (12 Grams) divided into three portions are administered at meal hours. The dose of Sm varies according to the severity of the disease and to the weight of the patient, from one gram twice per week to one gram daily. Bacterial resistance or drug toxicity to the above therapy requires the use of second-line drugs — pyrozinamide, ethionamide, cycloserine, isoxyl and viomycin. These agents are not less powerful, but have greater toxicity.

Isonoiazid is administered orally and is readily diffusible to all parts of the body including the central nervous system. Toxic effects are those affecting the central and peripheral nervous system. A peripheral neuritis is usually only seen when the normal daily dose of 300 mg. is exceeded.

Streptomycin is an effective antituberculous drug, but is less powerful. Parenteral administration by deep

intramuscular injection away from the sciatic nerve is necessary. Absorption into most organs in therapeutic concentrations is good, except that Sm crosses the blood-brain barrier only in meningitis. The optimum daily dose is one gram if long-term therapy is considered. A 100-pound patient is usually unable to tolerate one gram doses. The toxic effects are serious if they occur, but are reversible if the drug is discontinued upon early recognition. Vertigo is the most common complaint. Continuation of therapy may result in tinnitus and deafness. Urticaria, drug fever, dermatitis, bronchospasm, eosinophilia and aplastic anemia are also occasionally seen.

PAS is important as a companion drug to the more potent antituberculous drugs. Gastro-intestinal disturbances (e.g., nausea, vomiting, abdominal distension, reactivation of ulcers) and hypersensitivity reactions (e.g., dry scalp, pruritus and fever) are the predominant side effects.

Triple therapy is begun on all cases of presumably active tuberculosis. Occurrence of undesirable side effects requires the discontinuance of all drugs until the patient has recovered for several days. Desensitizing doses of INH should be commenced — one 50 mg. tablet initially, increasing the dose by 50 mg. daily to the optimum dose of 300 mg. daily. Once the patient is established on INH, start PAS in increasing doses and later Sm.

During the last few years, many studies have been completed comparing the results of double and triple drug therapy. There was very little difference in the results. The major argument for double therapy is that the addition of PAS to Sm and INH doubles the incidence of toxic effects. Those favouring triple therapy may argue that in daily practice, one is often confronted with the situation where one cannot be sure of the amount of previous chemotherapy, and where there may be primary or secondary resistance to one or more of the drugs. Another unknown factor is the percentage of recurrences in the future.

Steroids have found a place in antituberculosis treatment. They are given (1) in cases of severe drug reaction where there is insufficient time to allow slow desensitization, (2) in acutely toxic patients to decrease the tissue reaction to the disease, and (3) in children with meningitis.

Rehabilitation: Rehabilitation is important to provide a different job in cases in which the patient is unable to return to his former employment. Various academic courses are taught to those wishing to further their education.

Post-Sanatorium Care: Post-Sanatorium Care is necessary to make sure that recurrences do not occur. PAS and INH are taken for a total of 15 - 24 months by the average patient. A daily total of 14 hours of rest and sleep for the first three months is recommended. Patients are advised to return to work in three months, but may return earlier if they have minimal disease. The patient must return every three months for a chest film and a new drug supply for a total of two years.

Prognosis: The average duration of sanatorium care today is four months as compared with the eighteen months required fifteen years ago. The recurrence rate is about five per cent. The mortality has been decreased markedly, and consequently tuberculosis is no longer the dreaded disease which it was formerly.

SUMMARY

A practical discussion of the essential points in the diagnosis and treatment of pulmonary tuberculosis has been presented.

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Adolf Kussmaul

This great German medical physician of the nineteenth century was the first to describe the hyperpnea of diabetic coma. His medical experiences ranged from an army and country doctor to the position of professorship of medicine at Heidelberg, Erlangen, Freiburg and Strassburg. His contributions to medical science are varied and comprehensive. He differentiated the symptoms associated with mercurialism from syphilis, introduced the term, 'periarteritis nodosa', described the sign of paradoxical pulse as a resultant of obstructive pericarditis, described gastric tetany, and wrote a monograph on disorders of speech.

Kussmaul was horn in Baden near Karlsruhe in 1822. A career in medicine perpetuated the family interest in this field. His grandfather was a surgical dresser and an army surgeon. His father was also a military surgeon and later, took postgraduate training in anatomy, pathology and clinical medicine. At the age of 18, Kussmaul entered the University of Heidelberg to study medicine. In his final year, his thesis on the colour changes in the fundus of the eye won him a gold medal. On graduating, Kussmaul did extra studies first in Vienna under Hebra, Rokitansky and Skoda and later in Prague under Oppolzer.

Because of border skirmishes with the Danes in 1848, Kussmaul enlisted in the army in the Baden Battalion. One of the areas, Kandun, where he was posted while in the army, was the site where he set up a country practice after his discharge. However, his desire for further post-graduate training carried him back to the academic circles as a pupil of Virchow. In 1854 he received his Doctor of Medicine from the University of Würhurg. His first academic appointment was the Privadocent in Medicine at Heidelberg where he lectured on materia medica, toxicology, legal medicine and psychiatry. In 1856 he defined the cause of rigor mortis as chemical changes associated with disintegration of muscle.

In 1856, he received an appointment at Erlangen, and later at Freiherg. During this time he began to study and describe vascular changes in nerves, heart, and howel, and introduced the term, periarteritis nodosa. His interests also extended to the field of surgery and in 1868, he puhlished observations on the value of thoracenetesis in the treatment of empyema and pyopneumothorax. The procedure consisted of inserting a U-tube into the cavity and irrigating it with an antiseptic solution. Further in 1869, he published a treatise on the treatment of hypertrophy of the stomach through a new method using a stomach pump. He popularized the use of a stomach pump to alleviate pyloric obstruction.

Other fields of study included a description of gastric tetany, paradoxical pulse, hyperpnea of diabetic coma and speech disturbances. Since the name Kussmaul is known to medical students mainly because of his description of hyperpnea of diabetic coma, a excerpt from his observation follows:

"Since I have seen three diabetics in the course of a year die, with remarkably similar symptoms in which there was a peculiar comatose condition preceded and accompanied by dyspnoea, I believe that it is not merely a play of chance, but am of the option that it has to do with a form of death in diabetes which is rarely observed.

These conditions, with which all the patients reached the terminal stage, were essentially as follows:

1. A dyspnoea of un unusual kind. There is nothing here, as in ordinary dyspnoeas, to indicate that the air has to overcome the slightest obstacle on its way into or out of the lungs; on the contrary, it comes in and out with the greatest ease; the thorax widens itself splendidly in all directions, without any evidence of pulling in of the lower end of the sternum or the intercostal spaces; and a complete inspiration followed each complete respiration; down to the deepest part of the lungs, one hears a pure, loud and sharp vascular breathing (so called puerile breathing); and that all points to the highest degree of air hunger (Luft hunger) as does the oppressive pain of which the patient complains, which are so readily seen, the loud noise which the mighty respiratory and even stronger expiratory air stream produces in the larynx. . . .

In spite of the great distress, the dyspnoea did not become orthopnea." [1]

At the age of 66, Kussmaul retired from his post at Strassburg and returned to Heidelberg to receive the position of Professor of Medicine Emeritus. His 80th birthday was formally celebrated by the city of Heiedelberg and he was granted his title of Real Privy Councillor by the Grand Duke of Baden.

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The Investigation of Bronchogenic Carcinoma

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INTRODUCTION

This article is intended as a summary of the methods of investigating a patient suspected of having primary bronchogenic carcinoma, and, as such, will indicate most of the clinical, surgical and laboratory methods available to arrive at a diagnosis. At the present time, surgery is the only potentially curative form of therapy, so that some of the investigations listed will be of more value in pre-operative assessment than in diagnosis.

Perhaps the single most important lead to the diagnosis is suspicion, and this follows a good history and functional enquiry, paying attention particularly to sex, age, smoking habits, and respiratory symptoms. Usually the patient is a male around fifty years old who has smoked cigarettes many years. A chronic cough recently changing in character, recurrent chest infections, unresolving pneumonia, and hemoptysis are cardinal symptoms. It is important to always rule out neoplasm of the bronchus in the older person who has had pneumonia and it is often necessary to ask the patient specifically if he has noticed the four common chest symptoms of cough, sputum, fever, and pleuritic pain. The pneumonitis is of the obstructive type, where secretions are not cleared from bronchi as a result of loss of cilia following early malignant change in the mucosa.

The physical examination must be thorough and may be rewarding in demonstrating metastatic disease; this is important to know, since such cases are generally not considered surgical candidates, nor need they be subjected to extensive investigative procedures. Particular attention should be given to the pre-scalene areas. A valuable sign on listening to the chest is a constant wheeze not relieved by coughing.

Routine laboratory aids may be of value in sorting out the differential diagnosis, and one or more of the special skin tests may be indicated.

Special investigations will be considered under two headings, diagnosis and assessment for operability.

INVESTIGATIONS FOR DIAGNOSIS

We are primarily interested in diagnosing bronchogenic carcinoma early, for there is an increasingly better prognosis when the condition is recognized and treated in its very early stages, particularly in cases where there is a high degree of suspicion but no lesion demonstrable on plain chest radiographs.

A. Radiography

1. *Plain Chest Films: P/A and Lateral*

Repetitive mass radiography programmes have been unsatisfactory in revealing early chest neoplasms, and the prognosis in cases where a radiological lesion has been seen at the earliest possible time is not greatly altered. However, there is no doubt that the accuracy of radiological diagnosis is improved by the existence of previous chest films and their careful and thorough comparison.

An obvious chest lesion is a late radiological sign and usually the symptoms have been long standing by this time. Early radiological evidence of primary lung cancer may show by its secondary effects:

a) obstructive pneumonitis
b) segmental or lobar atelectasis
c) pleural effusion
d) increase in hilar shadow

2. *Pulmonary Tomograms*

Tomograms are radiographs taken at designated levels throughout the lung fields and are of value in defining the nature of a lesion. Generally it is necessary that a mass be present before tomograms are ordered so that the direction and level of the cuts can be gauged, but, on occasion, hilar and total lung tomograms may be carried out. Tomograms may suggest the extent of a lesion—its involvement of the mediastinal structures, pleura or chest wall—and will reveal cavitation and calcification, all of which are important pieces of information in the diagnosis and management of pulmonary lesions.

3. *Bronchograms*

In bronchography a radio-opaque dye, such as Hytrast, is sprayed into one or both bronchi and selective radiographs are then taken. The procedure may be done under local or general anaesthetic. It is important to remember that bronchography is employed in selected patients where a bronchial block exists, and should not be considered a routine investigation. It is of value in outlining the bronchial obstruction causing pneumonitis or partial atelectasis, and may well demonstrate the occult carcinoma.

B. Sputum Cytology

The most rapidly expanding technique employed in diagnosing bronchogenic carcinoma in its early stages

is the cytological study of sputum specimens. There are increasing numbers of cytologists and skilled technicians in this field and the facilities available are becoming more plentiful. It is fair to say that the future of successful diagnosis of bronchogenic carcinoma lies in sputum cytology, which is applicable as a screening procedure to detect the early lesions. Such screening should become routine, just as cervical smears for malignant cells. There are increasing numbers of patients who have no radiological evidence of tumour in the lungs but who have carcinoma cells within their sputum. Such cases of occult carcinoma have a vastly improved prognosis.

The reliability and accuracy of cyto-diagnosis depends on adequate specimens prepared and examined by an experienced cytologist. In general, a smear preparation is made, fixed in alcohol and stained by the Papanicolaou method. Several samples should be submitted to increase the accuracy of the results and these are best collected in the early morning. Sputum produced following a deep cough is usually adequate, but occasionally artificial stimulation of the cough reflex, or aerosols such as warm 50% prophylene glycol are needed to loosen the secretions.

With experience the cytologist can usually identify the type of carcinoma that exists, whether it be well differentiated, epidermoid, oat cell or anaplastic. This is of significance, because the prognosis in each type is somewhat different. For example, it is commonly believed that patients with the oat cell type are inoperable, resulting in an obvious influence in case management.

Sputum cytology studies in subsequently proven cases of bronchogenic carcinoma show a positive rate of 70% (58-83%) from six independent series, and the number of cases showing malignant cells but no other positive findings—the occult carcinoma—increases as sputum cytology becomes a screening procedure in the chest clinics.

C. Bronchoscopy

This is an extremely useful diagnostic procedure but its accuracy is only as good as the skill and experience of the bronchoscopist. A good examination includes noting the airway appearance and mobility, bronchial aspiration or washings, and biopsy where a lesion is seen or suspected. At the time of bronchoscopy it is frequently possible to decide what can be done for the patient; i.e., lobectomy, pneumonectomy, or if he is technically inoperable. Therefore, it is wise that the procedure be carried out by the surgeon who will be performing the operation.

Tumour involving the trachea or the carina and widening or fixation of the carina by mediastinal glands are evidence of doubtful resectability. Approximately 60% of central lesions are within reach of the bronchoscope. Most authors claim abnormal appearance suggestive of carcinoma in 45% of cases, and biopsies diagnostic of malignancy are reported to range from 25-85%.

The great value of bronchoscopy in diagnosis is in the occult carcinoma where there are malignant cells in the sputum but no radiological mass. Even the most minor abnormalities in the bronchus may be an early invasive or *in situ* carcinoma, and suspicions are multiplied when a patch of bloody, roughened mucosa is seen.

During bronchoscopy, direct bronchial aspirate, saline washings, or bronchial smears are obtained. Segmental washings have been used in a particular effort to isolate the involved lobe in cases of occult carcinoma, but no reliability can be placed on the segment of origin as a guide to the site of the lesion. Positive results from aspirates or washings are obtained in about 70% of the cases, which agrees well with figures for a positive diagnosis in sputum analysis. It is interesting to note that washings may be positive for malignancy, and the sputum not, and vice versa.

INVESTIGATIONS TO ASSESS OPERABILITY

There are many procedures reported for assisting the clinician to decide on the course of management of the patient who has cancer of the bronchus, but few of them are sufficiently reliable or practical to be considered almost routine. Some of the tests mentioned below are, in our opinion, more academic than useful, and others have very specific indications and limitations.

1. *Scalene Node Biopsy*

Biopsy of the scalene lymph nodes has enjoyed widespread popularity in the past in assessing patients for surgery, but there is increasing enthusiasm for an alternative method whereby a more reliable sample of the lymphatic drainage from around the airway can be examined. Biopsy of a palpable scalene node may be the only procedure necessary to diagnose bronchogenic carcinoma.

The scalene nodes are those lymph nodes which lie in the fat pad over the anterior scalene muscle in the triangular space bounded by the carotid sheath, the omohyoid muscle and the subclavian vein. Lymphatic drainage from the lungs is to these nodes, which are frequently involved in cases of advanced bronchogenic carcinoma. Disease in this area cannot be removed at surgery and, therefore, one cannot perform a curative resection.

In carrying out scalene biopsy an incision is made, under local or general anaesthetic, above and parallel to the clavicle. The incision is carried through the platysma and the deep cervical fascia exposing the scalene fat pad and its glands. Both fat pad and glands are removed and examined by frozen section. The glands

must be taken from the most medial site and should contain anthracotic pigment so that one is sure the nodes drain the lungs and not the head or neck.

Complications of the procedure are not common but include serous or chylous drainage, pneumothorax, mediastinitis, air embolism, and Horner's syndrome.

On the basis of anatomical studies of thoracic lymphatics, assumptions have been made that right-sided lesions drain to the right anterior scalene nodes, lesions in the left lower half lung field drain to either side, lesions in the left upper one half lung field drain to the left nodes only, and that mediastinal lesions drain to the side most involved. However, bronchogenic carcinoma seems to have proven these assumptions incorrect. Contralateral spread can occur from any area of either lung, and a unilateral biopsy is prone to give false negative results. Other causes of a false negative are failure to obtain a node which drains the lung, and blockage of proximal lymphatics by tumour, thereby preventing the extension of malignancy to these nodes.

2. *Mediastinoscopy and Mediastinal Node Biopsy*

With mediastinoscopy the surgeon can closely explore the mediastinum to determine lymphatic and mediastinal involvement by tumour. In the past decade this procedure has become popular in prethoracotomy assessment since both sides of the mediastinum can be viewed and biopsies taken.

Under general anaesthesia a low transverse suprasternal incision is made and carried into the perivisceral fascial plane of the neck. Blunt dissection is carried anterior to the trachea to its bifurcation. Direct palpation of pretracheal and paratracheal structures is possible, followed by the passage of a mediastinoscope for direct vision and node biopsy. Rare complications described are perforation of major vessels, pneumothorax and left recurrent laryngeal nerve palsy.

Independent authors report that extension of the tumour into the superior mediastinum is found on mediastinoscopy in approximately one-third of all patients deemed operable by the more common methods described and provides more precise information for the planning of the subsequent surgical management. Surgeons are now reporting that their rate of successful resections has been raised from 60% to 90% since mediastinoscopy has been employed.

3. *Pulmonary Angiography*

Angiographic study of mediastinal vessels may be used in selective cases considered potential candidates for curative thoracotomy to determine local extension of the carcinoma. Only hilar or closely situated mediastinal lesions are investigated in this way and, in particular, deformities of the right upper lobe may be differentiated from superior mediastinal lesions. The usual method is to cannulate a deep cubital vein under local anaesthetic, and whilst a radio-opaque dye is rapidly infused, radiographs are taken at three per second for twenty exposures from at least two directions. Expert radiological interpretation is necessary.

Angiographic evidence of non-resectability is shown by:

a) Partial or complete obstruction of the innominate vein or superior vena cava;
b) Invasion of the left or right atrium;
c) Involvement of the proximal two centimeters of major pulmonary veins;
d) Narrowing or occlusion of pulmonary arteries—the left pulmonary artery within 1.5 cm. of its origin and the right pulmonary artery proximal to its bifurcation.

A persistent filling defect is significant of invasion but it is well to recognize that displacement alone does not contraindicate surgery, since extrinsic pressure from enlarged nodes is not an uncommon finding. Irregular filling defects strongly suggest infiltration by tumour. The posterior aspect of the left upper lung root is often poorly defined unless the patient is rotated to the left anterior oblique, and this should be done for all cases with a lesion in the left lung.

Most centres using pulmonary angiography routinely report highly satisfactory results. Sanders *et al* in 100 cases recommended 42 for surgery on the basis of negative pulmonary angiograms and out of the 32 actually operated on, 29 (90%) were resectable. Wyman and Wilkins submitted 23 patients to thoracotomy and of 10 with negative angiograms, 7 (70%) proved resectable while 11 out of 13 (84%) with positive angiograms proved non-resectable.

It should be remembered that pulmonary angiography is not diagnostic, and is only of value in selected cases as a pretreatment assessment where it may spare many patients unnecessary operations.

4. *Needle Biopsy of Lung, Pleura and Pleural Fluid*

Needle biopsy of the lung under local anaesthetic with a Vim-Silverman needle directed under view of a bi-plane image intensifier is reported as 60% accurate, but the cases should be very carefully selected. If the case is one of a peripheral lesion and where open thoracotomy seems contraindicated, needle biopsy is useful in furnishing material for diagnosis. In a patient who is considered operable little is gained from lung biopsy by the needle method and exploratory thoracotomy should be undertaken without delay.

Needle biopsy of the pleura using an Abrahams punch needle under local anaesthetic is the method of choice and is indicated in pleural effusion or thickening of unknown etiology.

Visceral and parietal pleura may be involved by tumour to give fluid in the pleural space, or metastatic

seeding from septal lymphatic permeation may produce fluid. However, the commonest cause of effusion in cases of bronchogenic carcinoma is inflammation beyond the central site of the neoplasm, causing irritation of the visceral pleura. The fluid should be examined for malignant cells and only when a malignant pleural effusion is diagnosed is surgery considered not practical for curative purposes. Most bloody effusions are malignant, but bloody fluid is not an exclusive property of malignancy since false bleeding from inserting the needle often confuses the picture.

5. *Pneumomediastinography*

Further examination of mediastinal structures to evaluate the extent of tumour invasion can be achieved by outlining the vessels and airway with a gas. This is possible because of the perivisceral fascial envelope which invests esophagus, trachea, mainstem bronchi, aorta and extrapericardial pulmonary artery and pulmonary veins. Dissection of this natural fascial plane can be achieved by direct methods involving a percutaneous needle into the mediastinum through retrosternal, subxiphoid, paravertebral, transcervical, transtracheal or transbronchial approaches, or by indirect methods in which a gas is placed retroperitoneally via a presacral needle, and allowed to spread upwards into the mediastinum. A simple and more satisfactory approach is to introduce the gas into the mediastinum at the same time that scalene lymph node biopsy or mediastinoscopy is performed, using the same incision. Finger dissection exposes the fascial plane, a catheter is inserted and the wound closed. Carbon dioxide or oxygen is perfused under light pressure through the catheter, which is then removed and radiographs taken.

Failure to show tissue planes suggests a pathologic process, most likely that of invasive carcinoma, although inflammatory changes could cause similar obliteration. In the cases in which standard x-rays indicate hilar invasion, and, thus, non-resectability, pneumomediastinography may show that these, in fact, dissect off all central structures easily and suggest reassessment for thoracotomy. This procedure is not widely employed in North America as no precise information is given about the lesion, and other methods seem more accurate.

6. *Costal Intraosseous Venography (Azygography)*

The azygos venous system lies in the posterior mediastinum and may be of use in demonstrating abnormalities in this region when contrast medium is passed through it. The azygographic technique is one which allows roentgenological visualization of thoracic venous drainage. In only those cases with central lesions should azygography be considered. By putting a marrow biopsy needle into a rib in the same side and slightly lower than the level of the lung lesion, contrast media (60% Renografin) is injected under fluoroscopic control into the costal vein, azygos vein and superior vena cava. Spot radiographs are taken. Complete obstruction shows a retrograde flow of dye into ascending lumbar veins, collateralization on the posterior chest wall and vertebral plexus.

This procedure has few supporters. To get venous obstruction in the chest, the parietal pleura must be involved by tumour so that good radiographs and tomograms, plus pleural biopsy and fluid examination should achieve more than is to be learned from azygography.

7. *Circulating Cancer Cells*

Examinations of the blood for evidence of cancer cells is of doubtful value in diagnosis, but is believed by a few to have a place in indicating the appropriate therapy and possible survival rate. Several techniques are available, including simple Wright-stained smears of a centrifuged Buffey coat, and a millipore filtration method using Papanicolaou staining. The difficulty in examining blood for malignant cells lies in the differentiation of the cells from megakaryocytes and plasma cells. Hayata *et al* examined their lung cancer patients' blood repeatedly and obtained 33.5% positive rate, with the highest rate in cases presenting with hemoptysis.

The relationships between cancer cells in the blood and patient survival is interesting. Delarue *et al* in 270 cases of lung cancer showed 48% to have one or more positive samples, and that, following thoracotomy, only one-third of these patients with positive samples were alive after two years, whereas two-thirds of the cases with negative samples were alive with no evidence of metastases after two years. In another series of 208 cases subjected to resection, five year survival in the positive circulating cancer cell patients was 6%, and of negative sample cases 75% survived five years.

EXPLORATORY THORACOTOMY

With a large number of investigatory methods available for detecting the lung tumour, diagnosis does not often escape us. However, the peripheral pulmonary nodule, in particular, produces diagnostic problems, and recourse to exploratory thoracotomy may be necessary and, indeed, is often essential, since peripheral neoplasms are readily resectable with better prospects of cure. Exploratory thoracotomy is not frequently indicated in centrally situated lesions, but where a potentially resectable tumour is present, the surgeon may be justified in exploration. Gunn and Ross claim that exploratory thoracotomy with subsequent non-resection has no effect on the survival of the patient. They therefore recommend giving patients with suspected inoperable carcinoma of the lung the benefit of the doubt and exploring them with the hope of finding a resectable lesions. There are authors who advise against exploratory thoracotomy so that, at present, the decision is a personal one for the surgeon who must balance the patient's condition, the results of investigations and the prognosis.

CONCLUSION

In the treatment of cancer, the most important single factor is time of diagnosis. Most frequently neoplasms are discovered only after symptoms have been present for a long while and the disease is too widespread to be effectively managed. If there is any hope in the immediate future for persons who develop cancer of the bronchus, early diagnosis at a time before a mass is visible on plain chest films is essential. The prognosis is much more favourable in the cases of occult carcinoma than in other forms. In any 100 patients with bronchogenic carcinoma only about 50 are clinically operable at the time of diagnosis. If these 50 undergo thoracotomy, 20 of them will be non-resectable, and of the 30 who do have their tumour resected, only 25% will be alive in five years.

The investigations available to establish a diagnosis and to indicate appropriate therapy in cases of bronchogenic carcinoma have been outlined in this article, but each case should be not subjected to a rigid investigatory protocol. We have given the more commonly used procedures more emphasis, and have included others which in our opinion have extremely limited application but are of academic interest. In preparing this publication we have been impressed with the rapidly increasing value and accuracy of sputum cytodiagnosis in the earliest discovery of bronchial neoplasms. We feel that the family doctor who has a middle aged male patient with respiratory complications, must suspect bronchogenic cancer and will be offering more medical help to his patient if he at once has sputum specimens collected and sent to a cytologist. These should be repeated at regular intervals. Carcinoma-in-situ probably develops slowly, as it does in carcinoma of the cervix.

SUMMARY

Investigations for Diagnosis

A. *Radiographs*

1. Plain chest films—P/A and lateral
   Suspect a) obstructive pneumonitis
   b) atelectasis
   c) pleural effusion
   d) increase in hilar shadow
2. Tomograms
3. Bronchograms
   —selected patients with bronchial obstruction

B. *Sputum Cytology*

—repeated specimens of sputum
—most accurate, reliable and easiest routine screening procedure
—follow up in cases of occult cancer

C. *Bronchoscopy*

—airway appearance
—bronchial biopsy
—segmental washings, aspirate, smear

Investigations to Assess Operability

A. *Common*

1. Scalene Node Biopsy
2. Mediastinoscopy and node biopsy
3. Pulmonary angiography
4. Needle biopsy
   —lung parenchyma
   —pleura
   —pleural fluid
5. Barium swallow
6. Pulmonary function tests

B. *Uncommon*

1. Pneumomediastinography
2. Costal intraosseous venography
3. Circulating cancer cells

C. *Exploratory Thoracotomy*

Criteria of Non-Resectability

1. Inadequate pulmonary functional reserve.
2. Medical contraindications.
3. Distant metastases.
4. Pleural involvement with malignant effusion.
5. Positive scalene nodes.
6. Palpable mediastinal involvement or positive nodes in mediastinum.
7. Angiographic evidence of proximal vessel or atrial involvement.
8. Involvement of phrenic or recurrent laryngeal nerves, or the brachial plexus (Pancoast Syndrome) or the cervical sympathetics (Horners Syndrome).
9. Involvement of ribs, esophagus or opposite lung.
10. Tumour extension into trachea or carina.

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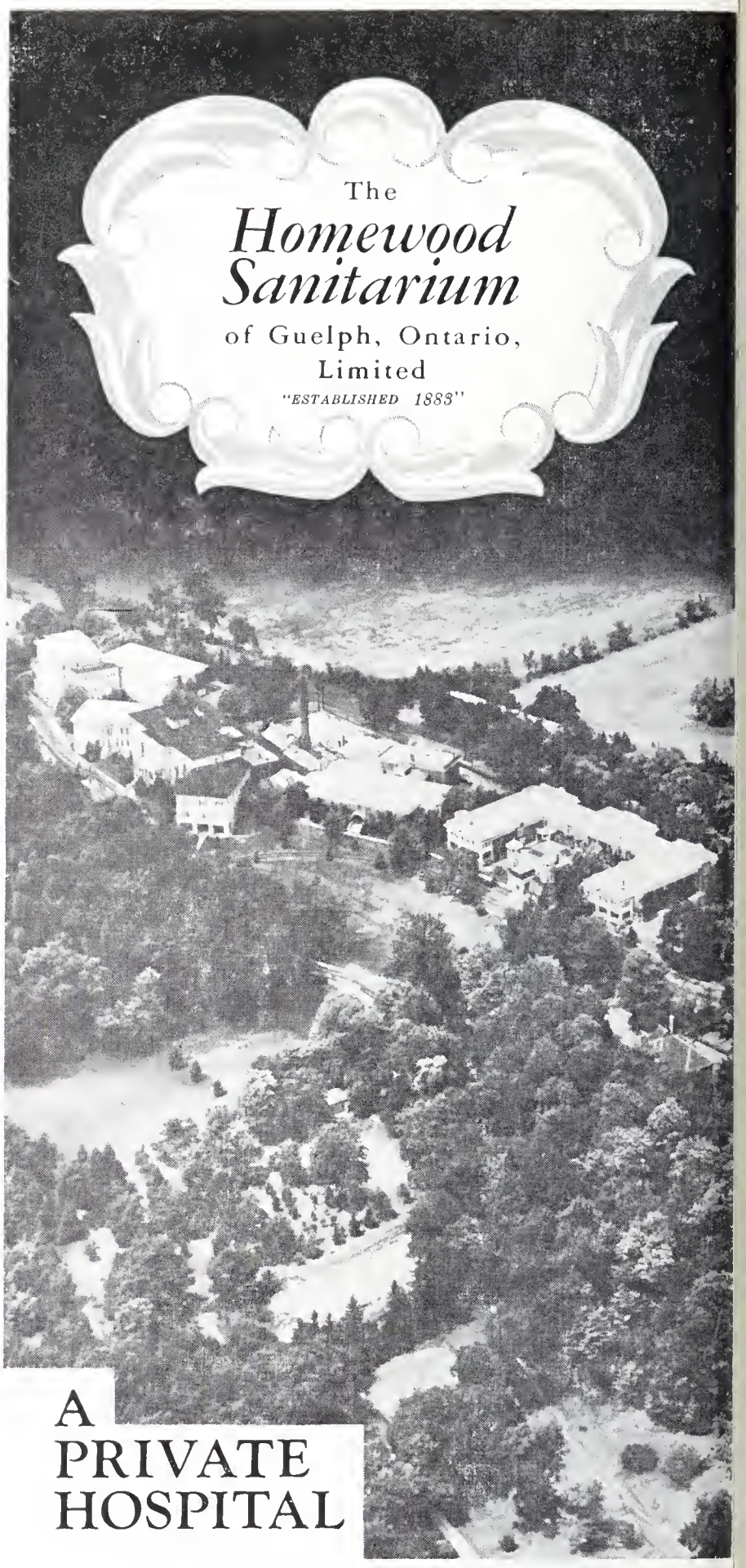

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Recent Advances

Radioisotope Scanning

Radioisotope scanning is the technique of mapping the distribution of gamma-emitting radioisotopic substances in the body by radiation detectors situated externally to the body and systematically moved so as to map out a predetermined area. Some of the methods are of proven clinical significance, while others are purely investigative. The radiation hazard is variable but in most cases not great.

BRAIN SCANS

Two radiopharmaceuticals are commonly used: (1) I^{131} albumen along with Lugol's iodine to prevent the uptake of liberated I^{131} by the thyroid gland; or, (2) Hg^{203} chlormerodrin. Projections used are anterior, posterior, and left and right laterals.

The usual criterion for diagnosis of an intracranial tumour is a localized area of increased count rate in at least two projections at right angles. Labelled albumen has a high blood level and consequently the vascular pattern may make interpretation more difficult. The accuracy in detecting tumours is between 70 and 90% and is higher for meningiomas, metastatic lesions and rapidly growing gliomas. Slowly growing gliomas and infratentorial tumours are difficult to diagnose and virtually no success has been reported in detecting brain stem or pituitary tumours by this method.

Lesions of the scalp, muscle, or skull, if associated with increased vascularity, may be detected; for example, Paget's disease of the skull, or scalp edema or hemorrhage.

Any localized lesion of the brain that alters the blood-brain barrier may be confused with an intracranial neoplasm. This includes arteriovenous fistula, subdural hematoma, pyogenic brain abscess, tuberculoma, granuloma, and cardiovascular accidents.

THYROID SCAN

A thyroid scan is indicated in the following situations: (1) any thyroid nodule without enough evidence to diagnose a benign disease; (2) suspected or proved primary or secondary carcinoma of the thyroid; (3) non-supressable I^{131} uptake in thyrotoxic patient.

A *cold* nodule indicates that the thyroid cells are not able to concentrate iodine. Although this is typical of carcinoma of thyroid, most cold nodules are benign.

Hot nodules are found in nodular goiter with a hyperfunctioning nodule, adenoma, carcinoma, and thyroiditis.

KIDNEY SCAN

For renal scans labelled mercurial diuretics are used (Hg^{203} or Hg^{197} chlormerodrin). Detection is based on retention of the label by the combination of mercury with the sulfhydral groups of enzymes of the renal tubular cells.

Various patterns have been observed: patchy uptake in renal insufficiency and many parenchymal diseases (eg., glomerulonephritis, pyelonephritis); space occupying lesion (tumour, cyst); contracted kidney (pyelonephritis); abnormal shape or position (pelvic or horseshoe shaped kidney); or complete failure to localize (severe renal failure).

LIVER SCAN

The agents which will localize in the liver are many and include I^{131} rose bengal which is taken up by the liver cells, colloidal Au^{190} and I^{131} aggregated albumin which are phagocytosed by the reticuloendothelial cells. Space-occupying lesions have been accurately diagnosed in 80% of cases, while in the same cases the liver function tests were abnormal in only 65%.

SPLENIC SCAN

Cr^{51} tagged red blood cells damaged by heat, specific antiserum, or by Hg^{203} labelled MHP, are injected into the patient. The spleen removes the damaged RBC's and, consequently, is outlined.

Indications for the use of this technique might include diagnosis of an obscure left upper quadrant mass, detection of accessory splenic tissue, and the accurate determination of splenic size (splenomegaly or the atrophy of sickle cell anemia).

BONE SCAN

Strontium follows the metabolism of calcium and is deposited in areas of osteogenic activity. In many cases, bone metastases may be detected prior to the appearance of x-ray changes.

LUNG SCAN

I^{131} aggregated albumen is temporarily trapped in the capillaries of the lung and gives a high concentration of radioactivity in the organ. The procedure will serve as an assessment pulmonary blood flow. Experimentally, this method will detect pulmonary infarcts in dogs and may be of use in humans in the differential diagnosis of pulmonary infarction and myocardial infarction. It may also be used in conjunction with pulmonary arteriography in the assessment of pulmonary blood flow, especially if serial studies must be performed.

MYOCARDIAL SCAN

Because of the equivocal results sometimes yielded by ECG and serum enzyme determinations, an additional

method to assess myocardial damage has been sought. Hg^{203} chlormerodrin concentrates in areas of tissue damage and scans demonstrate infarcts but the results are disappointing. Rubidium^{86} is similar to potassium and has a high concentration in heart and other muscle. With infarction it is released from damaged muscle cells in a similar way to potassium. This method also shows infarcts but is not reliable.

Recent work by Evans *et al* using labelled fatty acid appears to be superior to the Hg^{203} and Rb^{86} trials. Labelled fatty acids are taken up by heart muscle with their principal fates being carbon dioxide and the incorporation into tissue lipid (principally triglyceride and phospholipid).

BLOOD SCAN

I^{131} iodipamide remains in the circulatory system long enough to enable scanning of blood pools. Scans of the chest outline the heart and great vessels and are useful diagnostically when superimposed on a routine PA chest radiograph. This may distinguish a pericardial effusion and plain cardiac enlargement, be useful in the differential diagnosis of mediastinal masses, or demonstrate an aortic aneurysm.

PANCREATIC SCAN

Amino acids have a high specificity for the pancreas, probably because of the high rate of synthesis of digestive enzymes. Selenium^{75} has been substituted for sulphur in methionine in an effort to outline the pancreas. Pancreatic scans have demonstrated tumours and chronic pancreatitis but the accuracy of the method is still being evaluated.

PARATHYROID SCAN

Because of the great anatomical variability of the parathyroid glands (neck and anterior mediastinum) a method for the localization of parathyroid adenomas would be desirable. Thus far, no successful method is available.

WHOLE BODY SCAN

Functioning metastases from thyroid carcinoma occasionally have been detected by administration of I^{131}. Fe^{59} normally localizes in the pelvis, spine, and ribs. In cases with extramedullary hematopoiesis, localization is in the liver and/or spleen. In polycythemia rubra vera, in addition to the usual sites, spleen, proximal or distal ends of the femora are also involved. When Cu^{64} is administered to a patient suffering from Wilson's disease (decreased ceruloplasmin) there is a decreased rate of incorporation into ceruloplasmin and a heavy concentration in the liver and kidney.

SUMMARY

At present, radioisotope scanning is a clinically proven technique for the investigation of cerebral and thyroid disease, and many other possible applications are being investigated.

K.W.J.

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The Use of Computers for Medical Diagnosis

M. A. Nussbaum 6T5

INTRODUCTION

The use of electronic computers to make medical diagnosis is relatively new[1,2,3] and surprisingly little work has been done in this potentially important field. Because of the very limited experience and the not inconsiderable technical problems to be surmounted before computers can be employed routinely, their use in clinical medicine, though entirely feasible, is virtually non-existent to date. It is the purpose of this brief article to discuss and attempt to elucidate some of the theoretical and practical matters concerned in computer-diagnosis.

Can Computers be used for Medical Diagnosis?

Diagnosis is the identification of disease based on the information derived from the three areas of History, Physical Examination and Laboratory Investigation. Medical diagnosis is considered to be a logical process obeying certain basic principles. Computers can perform *any* process which is governed by a definitive set of rules. On this theoretical basis alone, one can say that computers are capable of making medical diagnosis. Once the process of medical diagnosis has been carefully analyzed and the essential logical elements picked out, there is really no reason why a computer cannot be programmed to make diagnoses following these elements as guide-lines.

Why Use Computers for Medical Diagnosis?

Even if we grant that computers *can* handle medical diagnosis, there still remains the problem of deciding whether computer-diagnosis is really worthwhile. What advantages are offered by computer-diagnosis?

If we consider those types of cases which the physician can diagnose upon first seeing the patient, the computer does not appear to have any evident advantages. However, it is probably true that in most cases seen clinically the diagnosis rests among several possibilities and is *not* immediately obvious. In this type of case, the computer could be extremely valuable in a variety of ways. The computer could name all the possible diseases when a particular group of symptoms and signs is present and give the actual probabilities for each disease being the correct one (using, for example, Bayes' Theorem as discussed below). No medical text, known to this author, gives multiple-attribute differential diagnosis. For example, what would be the differential diagnosis in a *30 year old male with right-sided chest pain lasting 10 minutes* and *heartburn brought on by exertion?* This type of question is really a central problem in clinical medicine, and, thus, this author feels that this is a very attractive and useful possibility with computer-diagnosis. Furthermore, the computer could indicate the diagnostic test(s) best able to differentiate among the possibilities and the therapeutic regimen in any particular disease which would be most efficacious. It must be appreciated that at present medical information is generally *not* in the mathematical form which can be used by a computer. Thus, in saying that the computer could do the above, I am assuming that the extensive preparatory data collection, which would be necessary, would be done and, indeed, a continuing process of data collection would be instituted so that data would always be up-to-date and valid.

Using computers for diagnosis could prove incidentally to be a valuable research tool and teaching aid to help further understanding and analysis of the process of medical diagnosis. Computer-diagnosis must, by its very nature, be entirely logical and objective, and, therefore, always reproducible (something that unfortunately cannot always be said for physicians' diagnoses). Inconsistences in a patient's total clinical picture will *never* be ignored by a computer, but clinicians with their "medical license" do so more often in making their diagnoses than is generally acknowledged. Computers can also be used to further medical knowledge by gathering statistical information on the relationship between diseases and attributes and carrying out research on the incidence and prognosis of diseases.

Because of the present phenomenal increase in medical knowledge (for example, in the areas of the pathophysiology of disease, diagnostic procedures and therapeutics), the individual practitioner is virtually overwhelmed and cannot effectively keep his knowledge up-to-date. No one in clinical practice can, after all, possibly afford the time to read all the relevant current medical literature in his specific areas of interest. Yet the fact remains that keeping up on new developments is the essence of good medical practice. The computer is admirably suited for the purely mechanical task of information-acquisition and cataloguing and is already being used for this purpose; e.g., for the Index Medicus by the National Institute of Health in the U.S.A. Computers can then serve, at the very least, an extremely useful role in the sorting out and dissemination of new medical information.

There appear to be real problems associated with the use of computers, namely, the cost of computer-

time (approximately $7.00 for one minute on the I.B.M. 7090 at the University of Toronto) and the availability of computers *per se*. It is felt by this author that a single centrally located computer could easily serve most large geographical regions. There is no need for each large clinic or hospital to purchase its own computer. There are certain facts which serve to temporize the "high cost" of computer-diagnosis. Computers would be immediately available twenty-four hours a day and equally alert at all times. Once properly programmed a computer could handle diagnostic problems very quickly; e.g., in a few seconds; so that the cost would decrease considerably. Computers being used for diagnosis might indeed save money in terms of "patient-days" in hospital by pointing quickly to the best diagnostic and therapeutic approach to difficult diagnostic cases. These patients currently tend to undergo a series of examinations by different consultants (which are often fruitless) and a battery of expensive laboratory tests in an attempt to uncover some abnormality and, thus, piece together a diagnosis.

Consideration of the Process of Medical Diagnosis

The process of medical diagnosis is composed of two basic steps—the first being Information-Acquisition and the second Information-Analysis. The former is the three-fold process of obtaining data from and about the patient relative to his illness through History (talking to the patient, relatives or friends), Physical Examination, and Laboratory Tests. The objective validity of data obtained varies in all three facets depending both on the doctor and the patient involved. For example, the accuracy of symptom-reporting varies as some patients "over-emphasize" symptoms, while others "under-emphasize" their symptoms. This is a function of the reliability of their observations, their psychological status, their intelligence, and their interaction with the physician. Some physicians are better, more patient, and more persistent history-takers than others, and certain physicians excel at picking up and recognizing the significance of physical signs on clinical examination. This is dependent on the experience, thoroughness, alertness and medical knowledge of the physician ("we only see that which we know"). The results of laboratory tests are the most objective of these three approaches, but even here the subjective element enters into the reported results of x-ray studies, biopsies, etc. Now, computers can be programmed to gather and store all of this clinical data so that it will be available for subsequent analysis and diagnostic formulation. Computers are obviously not of themselves going to alter the process of Information-Acquisition except to change the format of recording clinical data to make it easily transcribable to punch cards for input and storage in the memory of a computer. Computers may, however, prove to be of great value in the process of Information-Analysis. This is the logical integration and interpretation of all the previously collected data and the consequent arrival at a diagnosis (and the ordering of further tests, where indicated, to substantiate such a diagnosis). Most of the following discussion is, therefore, concentrated upon an analysis of Information-Analysis.

To begin with, some basic definitions are in order.

Attribute—is defined as any symtom, sign or finding on physical, x-ray, or laboratory examination. "Attribute-complex" is a particular constellation of attributes.

Disease—is defined as a unique "attribute-complex" caused by a single pathological process.

The *"critical combination" of attributes*—is defined as that combination accepted by general medical convention to be necessary for a particular diagnosis to be made; e.g., "Jones" criteria for Rheumatic Fever.

Medical diagnosis is a complex logical reasoning process. It involves, in essence, the matching up by the physician of the attributes which a patient possesses with the total mental picture of diseases which the physician possesses. This picture is derived from his colleagues' and his own clinical experience as well as from study of detailed textbook and medical journal descriptions of diseases. The provisional or "working" diagnosis made is the most likely attribute-complex/disease match. A definite diagnosis of any particular disease can only be made when the "critical combination" of attributes for that disease is present. Now any one attribute *per se* could be observed in a number of different pathological conditions. It is, however, the particular combination of attributes present which gives the physician insight as to the disease process(es) at work in the patient or, at least, reduces the disease which must be considered to be a reasonable number.

It must be emphasized that in actual practice each patient will only have some of all the possible attributes of any disease. There are a number of reasons for this. First, diseases may present in several different manners; e.g., incidentally in a routine check-up, or because of primary and secondary sequelae. This fact has an obvious bearing on the attributes which one could reasonable *expect* to be present in different patients who present at different stages in the evolution of a disease process. Second, attributes occur in association with a disease at varying levels of frequency. Some occur almost invariably with the disease, whereas others occur only rarely but have been authoritatively reported on occasion. Finally, it is of great importance to remember that a *patient* has a disease and the patient's variable psychological reaction to his disease can markedly shape the disease picture. The net effect of the preceding facts is the creation of difficulties in accurate diagnosis. On the one hand, patients with rather dissimilar attribute-complexes may, in fact, have the same disease, but on the other hand, patients with rather similar attribute-complexes may have different diseases.

These considerations help to justify on a practical basis the significance of attaining theoretical medical knowledge. The more medical knowledge and consequently the more complete and better picture of diseases a physician has, the better a diagnostician he will necessarily be. For the more disease entities which the doctor is able to keep under consideration as reasonable possibilities in each case, the more likely is he to be able to make the correct diagnosis. The necessity for making correct diagnoses in medical practice cannot be overemphasized because therapy can be given *rationally* only when the correct diagnosis is known. An example at this point may help to clarify matters. Suppose we were considering the following, grossly oversimplified situation.

Disease	**Attributes**
1. Pneumonia	Dyspnoea, cough, sputum, sharp transient lateral **chest pain** aggravated by coughing or breathing, fever, leucocytosis, sweating. (Positive sputum culture, positive x-ray and physical findings of consolidation)
2. Coronary Artery Disease	Deep retrosternal **chest pain** or pressure, with or without radiation, brought on by exertion or emotion and relieved by rest, lasting less than 15 minutes. Sweating, apprehension, E.C.G. changes. (S.T. elevation or depression) after exercise, pain relieved by nitroglycerine.
3. Hiatus Hernia	Deep retrosternal **chest pain** after meals, especially on lying down or bending over, heartburn, water brash, pain relieved by antacids. (Positive x-ray findings on barium swallow).

NOTE that bracketed attributes are the critical attributes; i.e., necessary for a diagnosis to be made. It is evident that in some cases the diagnosis would be evident—if critical attributes were present—but in others, a definitive diagnosis could not be established—as for example, with cough, deep central chest pain, fever, pain relieved by antacids—and a differential diagnosis would have to be made based on the probability of each disease being correct. (This might be done with Bayes' Theorem).

How Computers can be used to make Diagnoses

Attribute-complexes fall into one of the following three classes: a) complexes that are absolutely diagnostic; b) complexes that are diagnostically open-to-question (several diseases enter into the differential diagnosis, one of which is "most probable"); c) complexes that are unknown (no known single disease could account for the attributes). By far the majority of attribute-complexes fall into the second class, and, thus, the logical process of medical diagnosis can be stated, for all practical purposes, as a problem in conditional probability—"given the existence of a patient with the attribute-complex J, what is the most probable diagnosis?" One approach to the solution of this problem is through the use of Bayes' Theorem.[4] This well-known theorem can be used to calculate the conditional probabilities for different diseases being the correct diagnosis in a given patient and, in effect, to make diagnoses in this way. This is *not* the only manner of attempting to make diagnoses with the use of computers, but it is felt to be the most potentially valuable and, so, is the only one discussed here.

Bayes' Theorem, when used for medical diagnosis, can be written:

$$p(dx|sj) = \frac{p(dx) \cdot p(sj|dx)}{\text{Sigma } p(dk) \cdot p(sj|dk)}$$

Meaning of the various terms:

sj —is an attribute-complex consisting of s1, s2, s3 sr.

$p(dx|sj)$ —is the (conditional) probability of a patient's having a particular disease "x" when he has the particular attribute-complex "sj".

$p(dx)$ —is the ("a priori") probability of occurrence of disease "x" in the patient population under consideration.

$p(sj|dx)$ —is the probability of a patient's having the particular attribute-complex "sj" when he has the particular disease "x".

Sigma $p(dk) \cdot p(sj|dk)$—is the sum of this product calculated separately for each possible disease.

Discussion and Clarification

In simple terms what we are doing with Bayes' Theorem is translating statistical data on the incidence of symptoms and diseases into specific predictions of the probabilities that a particular patient has certain diseases. Implicit in the use of Bayes' Theorem is the assumption that all the attributes being considered are *totally* independent. Therefore, the attribute-complex sj is a combination of independent attributes s1, s2, s3 sr and the probability of the complex $p(sj|dx) = p(s1|dx) \cdot p(s2|dx) \cdots p(sr|dx)$ (where there are "r" individual attributes). Strictly speaking, for attributes to be considered independent with respect to one another, the presence of one attribut must *not* alter the probability of the presence of the other. However, this could only be true if all the attributes were randomly distributed throughout the population in *all* disease conditions, and then attributes would be of almost no value in diagnosis. Attributes must therefore for practical purposes be considered independent of one another if there is no direct causal relationship between them. Where there is a direct

causal relationship between attributes, one attribute *produces* to a variable extent another attribute. For example, if pleuritic chest pain were present it would necessarily follow that shortness of breath would be present 90% of the time. The presence of shortness of breath, then, would be essentially determined by the presence of the chest pain. In actual fact, the presence of two such attributes is generally due to the presence of some common underlying disease process and the attributes are, to all intents and purposes, independent. It is, however, necessary that the validity of this basic assumption, be tested for any given disease where sufficient data is present, using the chi-square test.

Another inherent assumption underlying the use of Bayes' Theorem is that the diagnostic possibilities under consideration MUST be *mutually exclusive*. Ordinarily this creates no difficulties. However, if two or more diseases are simultaneously present the computer could indicate this only by showing, for example, that two diseases had high and almost equal probabilities. As a possible way of overcoming this problem, one could state that where a patient is found to have more than one disease, the combination of diseases must be considered and treated as a new disease condition, with discrete attributes. This has, however, certain difficulties practically because of the infrequency in most cases of such disease combinations.

As a sort of corollary to this point, it is obvious that all patients selected as the basic source of clinical data must have only one disease. It must be stressed that the true incidence of attributes and diseases is not stationary but changes witih time, hence the necessity for continuous data collection and revision of the matrix of basic data periodically when using Bayes' Theorem.

One major objection put forward to the use of any set mathematical formula for medical diagnosis is the difficulty in "weighting" attributes with such a formula. That some attributes assume much greater significance than others to the physician in his consideration of every patient is unquestionably true. For example, the presence of extreme dyspnoea is far more important than a slight pain in the right thigh in the consideration of possible pneumonia. The more important and more heavily weighted attributes should be the *critical* ones involved, needless to say, but one is, unfortunately, not always sure of which are critical attributes at the outset. The problem of exactly quantitating such weighting is also very difficult, if not impossible, to solve at present, and will have to await extensive statistical analysis of the association of attributes and diseases. For example, is the presence of retrosternal chest pain aggravated by exercise one thousand times as significant as radiation of the pain to the neck in the diagnosis of coronary artery disease? The author, therefore, feels first that attributes should be weighted only if they merit added consideration, statistically, and second that this should be done according to some definite rules so that uniformity is achieved. Weighting done more or less indiscriminately, as at present, makes medical diagnosis illogical to a certain degree. For all of the above reasons, it is felt that weighting as currently employed in medical practice is more of a liability than an asset and no specific weighting device was employed with Bayes' Theorem. It should, however, be appreciated that Bayes' Theorem has to some extent a built-in weighting device in that the more commonly an attribute-complex is associated with a certain disease, the greater will be $p(sj|dx)$; i.e., the probability of that disease being present will be greater necessarily.

Only certain *critical attributes* are necessary to make a definitive diagnosis. Other attributes which may be present are, in effect, superfluous and serve only to round out the clinical picture and (perhaps) to *cement* a diagnosis already established. The absence of superflous attributes would, in fact, not change matters in a practical sense, though, to be sure, the conditional probability of the established diagnosis would be somewhat lessened.

The above paragraph leads to consideration of another very important point concerning medical diagnosis. The absence of attributes (other than superflous ones): i.e., *negative* attributes; often *is* just as important in making a certain diagnosis as is the presence of attributes; i.e., *positive* attributes. The absence of such attributes aids in diagnosis by making unlikely or completely ruling out alternative disease and, thus, narrows down the range of possible diagnoses. For this reason, programs should be written to include both positive and negative attributes in Bayes' Theorem. Otherwise, only attributes *actually present* would determine the diagnosis by influencing the probability of particular diseases. It must be emphasized that clinical diagnoses must often be based on very limited positive information, and the inclusion of absent attributes serves, therefore, to increase the available information to the computer (or clinician).

The usefulness of Bayes' Theorem is strictly limited in that, diagnoses cannot be made without a firm foundation of clinical information. There must be much careful data collection and analysis before one can use the Theorem for even experimental attempts at computer-diagnosis. For full-scale computer use, a monumental amount of work will have to take place.

Personal Experience with Computer-Diagnosis applied to Chest-Pain*

The matrix of information upon which the use of Bayes' Theorem was based was the collective information from 350 cases of chest pain accumulated over

* **This work was done under Dr. W. B. Spaulding in the Medical Out-Patient Department, Toronto General Hospital during the summer of 1964 with J. Schuman and B. Rasminsky (both Fourth Medical Year students, University of Toronto). The program was written by Miss Betty Clarkson of the Division of Statistics at the Toronto General Hospital.**

a period of several years. The information had been recorded by staff physicians on *pain-sheets* (Figure 1.) at the time of the patient's initial visit to the Out-Patient Department. The purpose of the pain-sheets was to characterize the pain as precisely as possible in a standardized manner; e.g., as to location, quality, periodicity, etc. One choice only could be checked for each characteristic. The 350 cases were arbitrarily divided into eleven diagnostic categories (Figure 2.) based on the clinical diagnoses made and the various mechanisms of chest pain.

Each category contained a number of diseases whose pain was thought to be due to a common cause; e.g., the category "Chest Wall Trauma" contained the conditions of chest wall strain, fractured ribs, etc.

The information contained on the pain-sheets was punched on I.B.M. cards; i.e., 1 card per pain-sheet. The information from these 350 cards as obtained by mechanical sorting served as the basic data in using Bayes' Theorem. This basic data was punched on I.B.M. cards; i.e., 1 card per pain characteristic (giving a total of 101 cards) in the following form:

Diagnostic Category No.	1	2	3	4	5		11
Squeezing Pain*	2**	0	0	2	20		4

Initially, the I.B.M. 7090 computer at the University of Toronto was used to work out the differential diagnoses for different interesting combinations of attributes based on the information from our 350 cases; e.g., *Retrosternal squeezing* pain in *males over 50*. To try to test the usefulness and accuracy of Bayes' Theorem for diagnosis, 45 additional chest pain sheets were obtained and the information punched on I.B.M. cards. Then, these 45 cases were subjected to diagnosis by the computer using Bayes' Theorem. The results were given as a differential diagnosis listing the actual probability of each diagnostic category. This attempt at computer-diagnosis was rather unrewarding in that only 11/45 or 24% of the cases were diagnosed in the correct group by the computer.

It cannot be too strongly emphasized that this degree of inaccuracy cannot be accounted for by simply stating that the principles upon which Bayes' Theorem is based are incorrect and, therefore, it cannot work in practice. The important point to keep in mind is that the inaccuracy of diagnosis may be due to the fact that the matrix of basic data upon which our probabilities and diagnoses are based may not be truly representative or reliaible and yet the method employed for diagnosis (Bayes' Theorem) may be prefectly sound. That is, the initial 350 cases may have been too small a sampling to form a really satisfactory basis for our clinical information and, thus, the computer would have difficulty diagnosing cases that were in any way atypical in their attributes. There are also several factors in the conduct of this study which might help to account for the inaccuracy found. To begin with, we were expecting the computer in many cases to be able to diagnose a case as belonging to a very heterogeneous group of diseases; e.g., "Other Respiratory Conditions", which included Lung Tumors, T.B., etc. As we had available a relatively small number of cases, the computer could not be programmed to diagnose INDIVIDUAL diseases as we ideally would have wanted. The amount of information made available to the computer was *very limited* being related only to the pain and involving no other symptoms which the patient might have had. Whether Bayes' Theorem can or cannot make accurate diagnoses consistently cannot be established, in any event, with any degree of assurance on the basis of this one small trial.

* **pain-characteristic**

** **number of patients in this category (1. Chest Wall Pain) with squeezing pain.**

Check one box in each column.

	(7)*		(8)		(9)		(10)	
Sharp	☐	1						
Dull	☐	2						
Burning	☐	3						
Crampy	☐	4						
Throbbing	☐	5						
Aching	☐	6						
Gnawing	☐	7						
Boring	☐	8	Superficial	☐ 1	Mild	☐ 1	Reliable	☐ 1
Squeezing	☐	9	Deep	☐ 2	Moderate	☐ 2	Vague	☐ 2
Other	☐	10	Other	☐ 3	Severe	☐ 3	Language Difficulty	☐ 3

Figure 1. A portion of a "pain-sheet" used in the Medical O.P.D. at the Toronto General Hospital. One square in each column must be checked.

* **Column number on "pain-sheet".**

DIAGNOSTIC CATEGORY	NO. OF PATIENTS
1. Chest Wall Pain	44
2. Chest Wall Trauma	19
3. Pneumonia and Pleurisy	16
4. Other Respiratory	24
5. Angina Pectoris	62
6. Esophagus	16
7. Other G. I.	11
8. Anxiety	58
9. Other Psychiatric	27
10. Other	33
11. Undetermined	40

Figure 2.

CONCLUSION

In conclusion, the author believes that, because of its great but as yet unfulfilled potentialities, work on computer-diagnosis warrants much more attention and investigation than it is presently receiving in the medical world. Physicians generally have conscious and unconscious fears regarding loss of jobs and decreased importance of their work when computer-diagnosis comes into existence, but these fears are basically unfounded for computers will aid physicians to do a better job and not displace them. The standard of medical care will be generally raised once computers are in use.

SUMMARY

The process of Medical Diagnosis is analyzed and the theoretical and practical bases for computer-diagnosis are discussed. Personal experience with the I.B.M. 7090 computer in the diagnosis of cases of chest pain is given briefly.

ACKNOWLEDGEMENT

The advice and assistance of Dr. W. B. Spaulding, J. Schuman, and Miss E. J. Clarkson in the preparation of this paper are gratefully acknowledged. I would like to thank my sister, Mrs. H. Reiss, for her patient and careful typing and re-typing of this paper.

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Physicians' Art Salon

The 1965 Physicians' Art Salon Committee now invites Canadian physicians and medical undergraduates to take part in the 21st running of the exhibition in Halifax, June 15th to 18th. As in the past, this feature of the CMA Annual Meeting is under the sponsorship of Frank W. Horner Limited, Montreal.

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Each exhibitor may submit up to three entries in the Fine Art and Colour Photography and four in the Monochrome Photography. Exhibitors may enter up to the limit in one or more sections. There is no charge. All costs, including transportation to and from Halifax, will be met by the sponsor.

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Book Review

MANUAL OF MEDICAL THERAPEUTICS

17th Edition. Department of Medicine, Washington University School of Medicine, St. Louis, Missouri. R. C. Packman and R. D. Utiger (Ed.) Little, Brown and Company, Boston, 1964. 272 pp. $5.00.

This manual, prepared in 1943 and revised every one or two years thereafter, was originally intended to complement the therapeutics conferences provided for Washington University medical students. At present, it has reached a stage where it could well complement such conferences at any medical school.

The manual does not pretend to be a complete textbook of therapeutics. Rather, it offers a concise, orderly presentation of the rationale and mode of therapy of the important medical conditions. The manual is abreast of recent advances, and can serve the practitioner as well as the student.

Of particular value are the various tables in which such complicated subjects as the chemotherapy of malignancy and the correction of dehydration are well summarized. The reader will also find that the chapter on the topical therapy of skin diseases, despite its brevity, suffices for the majority of the dermatologic conditions seen in the office. For the student, the manual should, however, prove must helpful as a handy reference to which he can turn for a capsule account of the modern treatment of the diseases with which he is expected to be familiar.

The only real shortcoming of the manual lies in the general omission of the investigative procedures necessary for the disease entities discussed. However, this is not the purpose of the manual, and for those who are interested in how to treat a given disease, once the diagnosis has been made, this manual will be of great value.

K.H.S.

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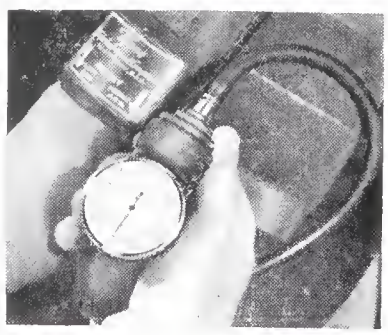

Taylor Instruments **MEAN ACCURACY FIRST**

Abstracts

Circulating "Cancer Cells"

Delarue, N. C. et al. Arch. Surg., 89: Aug. 1964.

Many workers have been puzzled and fascinated by the pathological and clinical significance of certain cells found to be circulating in the peripheral blood of patients known to harbor malignant diseases of infinite variety.

This paper summarizes the results obtained in a series of 270 cases of malignant disease in which 48% of the cases yielded one or more samples of demonstrable *malignant* cells in the blood. At the same time, 24% of patient without clinical evidence of malignant disease, who were subjected to surgical treatment, also showed *positive* sampling. A two to five year follow-up of these patients appears to indicate that there is a correlation between the presence of these abnormal cells and the patient's subsequent history of recurrent disease.

In conclusion, the authors state that, until more refined methods of assessment are available, any speculation of the true frequency or the actual significance of circulating cancer cells in the peripheral blood must be regarded with caution.

D.A.D.

Calcifications of the Heart

Holmes, R. B. J. Can. Ass. Radiol., 15: 163-176, Dec. 1964.

The recognition of distinctive locations and radiological appearances of cardiac calcifications is becoming a useful technique in diagnosis and selection of treatment of heart disease. Calcifications in the heart are sometimes metastatic and are associated with increased availability of calcium and calcifications in other organs. More commonly, lesions are due to dystrophic calcifications in slowly metabolizing tissues and are, therefore, seen in devitalized areas. Calcified lesions are seen in the form of plaques, linear streaks or nodules and these are most efficiently recognized by image intensifiers with cine film recording and by specific positioning of the patient.

Lesions of the pericardium, myocardium, coronary arteries and the four valves have been described verbally, diagrammatically and by means of roentgenograms to facilitate their recognition by their specific calcification patterns. The importance of this technique is threefold:

a) to confirm a doubtful clinical diagnosis;

b) to allow more accurate prognosis;

c) to select management of the patient; the choice of operative procedure may depend on the presence or absence of calcification.

M.T.

Abstracts

Comparative Protein Studies of Normal and Abnormal Meconium

Schachter, H., Dixon, G. H. Can. J. Biochem., 43: 381-397, 1965.

Starch gel electrophoresis and immunoelectrophoresis were used to compare the protein composition of normal meconium and that from meconium ileus patients. Different electrophoretic patterns were observed but it was shown that enzymatic digestion of meconium ileus meconium by trypsin and chymotrypsin can convert the abnormal pattern to a normal one. It is suggested that all fetal gastrointestinal tracts contain meconium ileus meconium but the disease develops only when intestinal proteolysis is defective.

Phenol extractions also showed that meconium ileus meconium does not contain an abnormal mucoprotein which may be responsible for its viscosity. The consistent differences between normal and abnormal meconium are probably due to partial proteolysis in the digestive tract and not related to cystic fibrosis.

M.T.

Recurrent Otitis Media and Croup in Children

Fearon, B. Appl. Therap., 6: 729-732, Sept. 1964.

Otitis media is divided into two clinical types: inflammatory, secondary to bacterial or viral invasion, and non-inflammatory or secretory, due to mechanical obstruction of the eustachian tube. Inflammatory exudation is most frequently secondary to infected adenoids and tonsils, but other factors may contribute. It may proceed to suppuration, bulging of the tympanic membrane, and spread to and damage of the mastoid air cells with possible rupture of the drum itself. It must be treated with antibiotics and decongestants, and often by myringotomy to relieve pain and prevent extension. Tonsillectomy and adenoidectomy are performed in recurrent cases. The latter operation must never be deferred in a small child simply because of his age. Secretory otitis media is almost always due to allergy with secondary edema resulting in eustachian tube obstruction. Nasal decongestants are most important in the treatment of acute cases, while adenoidectomy usually relieves recurrent attacks.

Croup presents either as acute laryngotracheitis or acute supraglottitis, both inflammatory conditions of the laryngeal airway which may quickly end in asphyxia. Relief of airway obstruction is most important either by orderly tracheotomy in the operating-room or by immediate emergency stab tracheotomy, if the child's life is in danger.

M.T.

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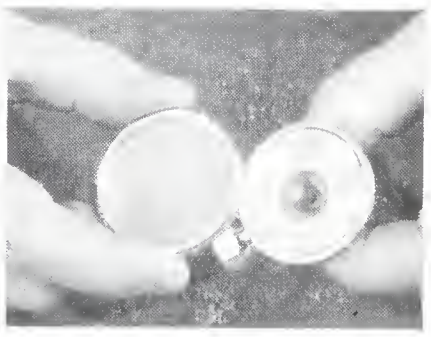

Taylor Instruments **MEAN ACCURACY FIRST**

Abstracts

Multifactorial Inheritance in Diabetes

Simpson, N. E.: Diabetes 13: 462-471, Sept. 1964.

An extensive study of diabetics and their relatives leads the author to suggest a multifactorial rather than a "single locus" inheritance pattern of diabetes. 13,009 relatives of 2,645 diabetic probands were studied and the incidences of diabetes in children of diabetic parents and in first degree relatives of diabetics were compared with normal controls.

The recessive hypothesis could explain the data for children whose parents are both diabetics but multiple genetic factors are suggested in first degree relatives and these factors may be different in diabetics with different age of onset. Multifactorial inheritance is compatible with both sets of data.

In her discussion, the author compares human and animal studies and correlates some of her findings with physiological and biochemical etiological factors which support the hypothesis of multifactorial inheritance of diabetes.

M.T.

Causes of Blindness in Canada

MacDonald, A. E.: Can. Med. Ass. J. 92: 264-279, Feb. 1965.

This, the most comprehensive survey of blind persons in Canada, was based on registrations with the Canadian National Institute for the Blind. Over 24,000 people in all age groups were included and the causes of blindness were classified according to the site and type of lesion and the etiological factors.

The most frequently involved site was the globe itself (e.g. glaucoma, myopia, phthisis) but the retina, the lens and the optic nerve were also commonly affected. 32% of the blindness was traced to prenatal causes while the most important postnatal factors were metabolic and infectious diseases and traumatic injuries.

The incidence of blindness in Canada was found to be 131 per 100,000 but serious ocular disease is four times more prevalent and 101,346 such severely affected cases were registered with the C.N.I.B.

M.T.

Massive Hemorrhage Following Small Bowel Biopsy

Vidinli, M., Finlay, J. M.: Can. Med. Ass. J. 91: 1223-1225, Dec. 1964.

This case report describes an instance of massive GI hemorrhage following small bowel biopsy and serves to emphasize one possible risk of the procedure.

The clinical and investigative value of the technique is confirmed by its increasing use in the diagnosis of GI tract disease. The reported incidence of serious complications is low. 159 similar biopsies had been performed over the last three and one half years prior to this incident, with no serious complications. But the authors point out that small bowel biopsy is a blind procedure and the risk of hemorrhage must be considered. Care should be taken to avoid excessive suction on the biopsy device when obtaining the mucosal specimen. Routine laboratory absence of bleeding tendency should be established.

The authors conclude that the incidence of massive hemorrhage will remain low if adequate technical care is taken and clinical precautions are observed.

D.A.D.

Surgical Management of Transposition of Great Vessels

Mustard, W. T., et al. J. Thor. Cardiovasc. Surg., 48: 953-958, 979-983, Dec. 1964.

This presentation outlines a method of total correction as a two stage procedure. It was pointed out that the infant born with transposition of the great vessels rarely survives the first year of life. Total correction in this age group is a surgical feat and partial procedures leave one with a handicapped child.

The two-staged procedure of total correction outlined is as follows: The first stage involves the creation of an atrial septal defect as suggested by Hanlon and Blaloch in 1948. The second stage, carried out in the second or third year of life, is a practical application of principles proposed by Albert in 1954. A baffle of pericardium is sutured in place directing the pulmonary venous return into the right ventricle and the systemic venous circulation into the left ventricle. This is done in such a way that the artrial chambers can grow with the child and ensures relatively normal atrial hemodynamics as the circulatory demands increase.

D.A.D.

On Inspection - Answers

1. The pathological conditions which may result in an isolated pulmonary nodule may be classified as follows (after Levine E. R. and Froman A., Roentgenology of the Chest. Rabin, C. B. ed. Published by Thomas, Springfield Illinois, 1958):

I. NEOPLASMS

A. Malignant

1. *Primary*

a) bronchogenic carcinoma
b) sarcoma

2. *Secondary*

a) carcinoma
i) hypernephroma
ii) carcinoma of nasopharynx
iii) carcinoma of colon
iv) chorioepithelioma
v) others

b) sarcoma

B. Benign

1. Hamartoma
2. Adenoma

II. INFLAMMATORY LESIONS

A. Granulomatous

1. *Tuberculosis*

a) encapsulated caseous focus
b) calcified focus
c) encapsulated emphysema

2. *Mycotic*

a) histoplasmosis
b) coccidioidomycosis

B. Localized pneumonia

C. Abscess

D. Gumma

III. CYSTS (FILLED WITH FLUID)

A. Congenital cysts and A-V fistulae

B. Echinococcus

IV. FOREIGN BODIES

V. ARTIFACTS AND CHEST WALL LESIONS

A. Nipple Shadow

B. Pigmented Mole

C. Abscess of chest wall

D. Neoplasm of rib

The patient in Figure 1 proved to have tuberculosis. The absence of calcification, the rather irregular outline and no fluid level in this lesion is usually more characteristic of a malignant lesion.

2. The film of Figure 2 illustrates a left pneumothorax, with a right chylothorax and right phrenic nerve paralysis. Pleural fluid may be a transudate, exudate (serous effusion), empyema, chylous effusion or rupture and blood. Chylous effusions may be caused by trauma to the chest with or without associated fractures, accidental severance of the thoracic duct or its tributaries (vis. stomach and gall bladder surgery), perforating lymphangitis, aneurysm of the duct with rupture and obstruction. Obstruction of the duct may be due to neoplasm, filariasis, thrombosis of the subclavian vein and cirrhosis of the liver. Some are of unknown aetiology.

Phrenic nerve paralysis may result from

A. Birth trauma

1. cervical stretching (breech delivery)
2. abnormal intrauterine position

B. Infections and Inflammations

1. poliomyelitis
2. diphtheria
3. mediastinal pleurisy
4. pericarditis

C. Pressure on the Nerve

1. *Inflammation (usually lymph node involvement)*

a) syphilis
b) sarcoidosis
c) tuberculosis
d) erythema nodosa
e) silicosis

2. *Tumours*

a) primary and secondary malignancy of lung
b) primary and secondary malignancy of mediastinum
c) substernal goitre

3. *Blood vessels*

a) aneurysm

D. Miscellaneous

1. *Nerve toxins*
2. *Spontaneous rupture*
3. *During anaesthesia*
4. *After abdominal operations*

3. A reasonable differential diagnosis of the multiple discrete, round, calcified lesions would include healed miliary tuberculosis, and miliary calcification in histoplasmosis. Less commonly one may see a picture which would resemble this one in nodular silicosis, stannosis, baritosis, pulmonary calcinosis in scleroderma, haemosiderosis and in one type of sarcoid. This patient's tuberculin test was strongly positive. A culture of aspergillosis was grown from his sputum. However, as aspergillosis is a frequent contaminant of sputum culture, a diagnosis of secondary aspergillosis infection superimposed on an inactive tuberculous process has to be regarded with some scepticism. One report from Veterans Hospitals in the U.S. showed that in a large series of 887 resected *solitary* pulmonary nodules, granulomas constituted 53% of the nodules and of these, 25% were due to histoplasmosis and 20% to tuberculosis. While these figures are not directly applicable to Ontario, they serve to illustrate that fungal infections, and particularly histoplasmosis, deserve diagnostic consideration in all lung pathology.

4. This man operated a stapling machine and used to hold the staples between his teeth. He probably accidentally aspirated one of those staples, which in this case lodged in the right lateral basal bronchus. Even though asymptomatic, because of the risk of secondary infection or obstruction at some later date, the position of the foreign body should be determined by AP and lateral chest X-ray and the object then removed via the tracheal route. Postoperatively, a staple diet is contraindicated in this patient.

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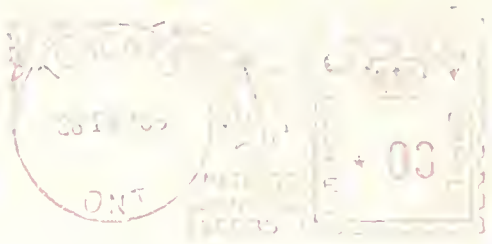
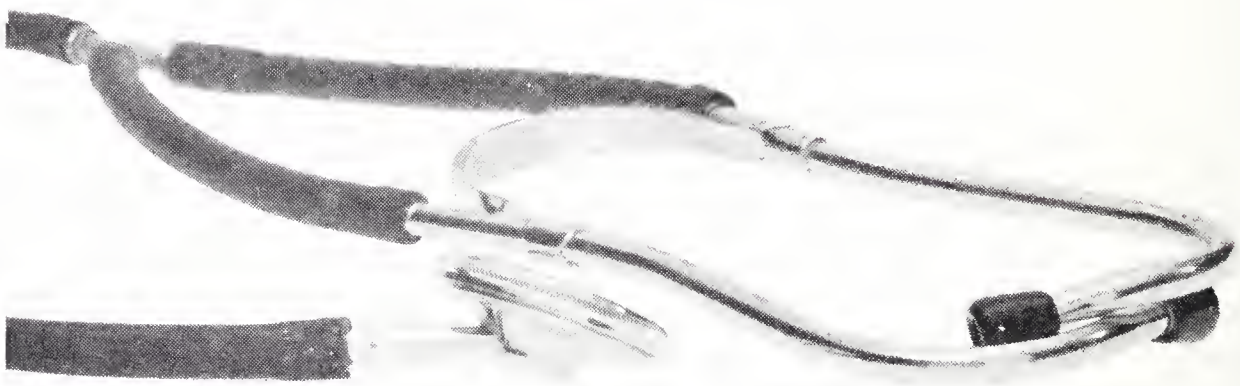


The sounds of life –now your challenge



The many sounds and rhythms of life now have your ear. Your skills are challenged . . . to modulate discordant tones, to maintain healthy ones.

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